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(C07D513/04, 281:00, 239:00)

(54) Sulfur-containing fused pyrimidine derivatives, their production and use

Schwefel enthaltende kondensierte Pyrimidinderivate, ihre Herstellung und Verwendung

Dérivés de la pyrimidine condensés contenant du soufre, leur préparation et utilisation

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(73) Proprietor: **Takeda Chemical Industries, Ltd.**
Chuo-ku, Osaka (JP)

(72) Inventors:

- Naka, Takehiko
Kobe, Hyogo 658 (JP)
- Saijo, Taketoshi
Ikeda, Osaka 563 (JP)
- Shimamoto, Norio
Kobe, Hyogo 658 (JP)
- Suno, Masahiro
Kobe, Hyogo 654-01 (JP)

(74) Representative: **Laredo, Jack Joseph et al**
Elkington and Fife
Prospect House
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

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- ARZNEIMITTELFORSCHUNG, vol. 32(I), no. 6, June 1982, pages 610-612, Editio Cantor, Aulendorf, DE; R. KAUL et al.: "Identifizierung eines dritten S- haltigen Metaboliten von 1-Allyl-3,5-diethyl-6-chloruracil und Bildungsmechanismus der SCH3-Metaboliten"
- CHEMICAL ABSTRACTS, vol. 81, no. 13, 30th September 1974, page 458, column 1, abstract no. 77869v, Columbus, Ohio, USA; Y. MAKI et al.: "Smiles rearrangement. XIV. Novel reactions of 1,3-dimethyl-5-nitro-6-chlorouracil with 2-aminothiophenol", & CHEM.PHARM.BULL.1974, 22(6),1265-8
- JOURNAL OF ORGANIC CHEMISTRY, vol. 44, no. 26, December 1979, pages 4877-4880, Columbus, Ohio, US; R. RICHTER et al.: "5-Aryl-7-(N-arylcarbamoyl)-4,6-dioxo-2,3,3a,4,5,6-hexahydrooxa(thia)zolo[2,3-c]pyrimidines and 3-(N-arylcarbamoyl)-2,4-dihydroxyquinolines from 2-methyloxa(thia)zoline and aryl isocyanates"

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Description**BACKGROUND OF THE INVENTION**

- 5 The present invention relates to novel sulfur-containing fused pyrimidine derivatives useful as medicines.
- Autacoids which are produced *in vivo* exhibit various pharmacological actions in the small amounts thereof which are liberated from cells by stimulation of some kind, and act on cells and organs in the vicinity of production sites thereof to play an important role in the expression, the maintenance and the regulation of various physiological functions.
- Vascular endothelial cells produce various biologically active substances, thereby regulating vasoactivity and hemocyte functions. In particular, prostacyclin (PGI₂) and endothelium-derived relaxation factors (EDRF) have been noted as factors for relaxing vascular smooth muscles. It has recently been found that one of the endothelium-derived relaxation factors is nitrogen monoxide (NO) or an analogue thereof.
- On the other hand, it was also reported that the endothelial cells produced the factors for constricting vascular smooth muscles (EDCF) under various stimulation conditions such as anoxia. In 1988, M. Yanagisawa et al succeeded in isolating a vasoconstrictor substance from the culture supernatant of the endothelial cells of porcine aortae [M. Yanagisawa et al, *Nature* 332, 411 (1988)]. This substance, consisting of 21 amino acid residues and 2 intramolecular disulfide bonds, was named "endothelin (ET)". The endothelin strongly contracts various smooth muscles (such as tracheal smooth muscles) including vascular smooth muscles (such as coronary arteries, aortae and basilar arteries) of animals including humans. The activities are more than 10 times as strong as those of known constrictor peptides such as angiotensin II, vasopressin and neuropeptide Y, and it is not affected by receptor antagonists or synthetic inhibitors of known vasoactive substances such as serotonin, norepinephrine, thromboxane A₂ and leukotriene. It is known that only calcium antagonists partially inhibit their activities. It has recently become clear that the endothelin has not only smooth muscle constrictor activity, but also various physiological activities. For example, the endothelin promotes secretion of atrial natriuretic peptides in cultured rat atrial muscles, and inhibits renin secretion from juxtaglomerular cells. However, it is not entirely revealed till now what physiological role endothelin plays *in vivo* and what pathology endothelin is concerned with. Considering the various activities of the endothelin and the distribution of endothelin receptors over a wide range from vascular vessel systems to brains, the endothelin might relate to various diseases such as renal, pulmonary and cardiac diseases. It is further anticipated that the endothelin acts as a hormone or an autacoid controlling circulation or as a neurotransmitter.
- 30 Nerve growth factor (NGF) is a polypeptide having 118 amino acids. NGF is a neurotrophic factor necessary for differentiation and survival in peripheral, sensory and central neurons. In the brain, NGF is distributed in the cerebral cortex and hippocampus, and acts as a neurotrophic factor for cholinergic neurons in the basal forebrain. In the case of patients suffering from Alzheimer's disease, degeneration of cholinergic neurons in the basal forebrain is significantly involved, and it is believed that the impairment of learning and memory as a result of the disease is due to this degeneration [M. Goedert et al., *Mol. Brain Res.*, 1, 85-92 (1986)]. Recently, it has been reported that, in various animal models with cerebral lesions, NGF prevents the degeneration of cholinergic neurons and reduces the impairment of learning and memory [F. Hefti, *J. Neuroscience*, 6, 2155-2162 (1986); V. Pallage, *Brain Res.*, 386, 197-208 (1986)]. From these findings, NGF appears to be the most effective candidate for the treatment of Alzheimer's disease.
- On the other hand, interleukin 1 (IL-1) known as an inflammatory autacoid is produced and secreted mainly in stimulated monocytes or macrophages. Recently, it has been shown that IL-1 can be produced by many types of cells including endothelial cells or fibroblasts.
- Furthermore, IL-1 acts on various types of cells and is involved in many functions. First, in relation to immune or inflammatory reactions, IL-1 causes lymphocytes, T and B cells, to differentiate or to proliferate, increasing their production of cytokines such as IL-2 or CSFs. IL-1 acts on endothelial cells and plays an important role in fibrinogenesis or lymphocyte adhesion, and also acts on hepatocytes to make acute phase proteins. Second, IL-1 relates to connective tissue cells, and causes fibroblast or synovial cells to proliferate. However, IL-1 induces protease production and reduces the extracellular matrix proteins on these cells, causing tissue damage. Similarly, IL-1 acts on chondrocytes or bone cells. Third, the action of IL-1 on nervous cells is also becoming clear.
- 50 **SUMMARY OF THE INVENTION**
- We have therefore sought, in accordance with the present invention, to provide compounds useful for the treatment and prevention of various diseases induced by abnormalities in regulation of various reactions *in vivo* mediated through endothelin or interleukin 1 of various autacoids produced *in vivo*, for example, diseases such as myocardial infarction, angina pectoris and renal failure, and various immune diseases and inflammatory diseases, as well as rheumatism, by inhibiting the above-mentioned reactions *in vivo*.
- A further object of the present invention is to provide compounds useful for the treatment of cerebral lesions and memory impairment (for example, in Alzheimer's disease) through inducing the production of NGF.

Other objects of the present invention will become apparent from the following description.

The present inventors conducted intensive investigations to provide compounds useful for the treatment and prevention of diseases such as myocardial infarction, angina pectoris and renal failure, various immune diseases and inflammatory diseases, and cerebral lesions and memory impairment (for example in Alzheimer's disease), and discovered that certain specific sulfur-containing condensed pyrimidine derivatives could attain these objects, thus arriving at the present invention.

In accordance with the present invention, there is provided a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof:

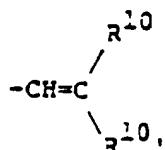
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wherein R¹ represents an alkyl group of 1 to 8 carbon atoms or alkenyl group of 2 to 8 carbon atoms which may be substituted by cyano, carbamoyl, pyridyl, quinolyl, hydroxyl, C₁ to C₄ alkoxy, amino, C₁ to C₄ alkyl, carboxyl, C₁ to C₄ alkoxy-carbonyl or C₂ to C₆ alkanoylamino groups, (2) an aralkyl group, which is obtained by combining a phenyl or naphthyl group with an alkylene group of 1 to 4 carbon atoms, in which the phenyl or naphthyl group may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, phenyl, o-cyano-phenyl, methoxy, ethoxy or nitro or (3) a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, methoxy, ethoxy or nitro groups; R² represents (1) hydrogen, (2) an aliphatic hydrocarbon group of formula:

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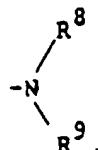
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wherein R¹⁰ represents a cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl, R¹¹ represents a C₁ to C₈ alkyl, phenyl, naphthyl, cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl group, and R¹² represents dimethylamino, diethylamino, morpholino, piperidino or piperazine, (3) a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, methoxy, ethoxy or nitro group, (4) an unsubstituted or substituted amino group of formula:

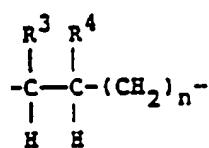
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wherein each of R⁸ and R⁹ is hydrogen, an alkyl group of 1 to 8 carbon atoms or a fatty acid-derived acyl group of 1 to 8 carbon atoms, (5) a formyl group, (6) a nitro group or (7) a halogeno group; A represents a saturated or unsaturated divalent hydrocarbon chain of 2 to 4 carbon atoms selected from (1) a group of the formula:

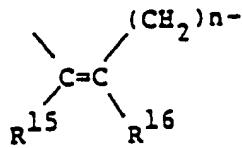
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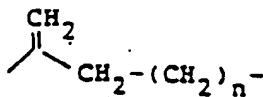
wherein R³ represents (1) hydrogen, (2) C₁ to C₄ alkyl which may be substituted by an halogen atom, or an C₁ to C₄ alkylthio or phenylthio group, (3) -YR⁵ wherein Y is -O- or -S- and R⁵ is hydrogen, C₁ to C₄ alkyl or a phenyl or naphthyl group which may be substituted by C₁ to C₄ alkyl, C₁ to C₄ alkoxy or phenyl, which may be substituted by 1 to 3 halogen atoms, or a fatty acid-derived acyl group of 1 to 4 carbon atoms; R⁴ represents hydrogen or an alkyl group of 1 to 4 carbon atoms; and n represents an integer of 0 to 2, (2) a group of the formula:

5



wherein R¹⁵ and R¹⁶ represents hydrogen, C₁ to C₄ alkyl, -COOR¹⁷ wherein R¹⁷ is hydrogen, C₁ to C₄ alkyl or NHR¹⁸ wherein R¹⁸ is hydrogen, C₁ to C₄ alkyl or C₁ to C₄ alkanoyl; and n represents an integer of 0 to 2 or (3) a formula:

10



15 wherein n represents an integer of 0 to 2; and m represents an integer of 0 to 2.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

20 Of the sulfur-containing condensed pyrimidine derivatives included in the present invention such as thiazolo[3,2-c]pyrimidine-5,7(6H)-diones [carbon number of chain A is 2], pyrimido[6,1-b][1,3]thiazine-6,8(7H)-diones [carbon number of chain A is 3] and pyrimido[6,1-b][1,3]thiazepin-7,9(8H)-diones [carbon number of chain A is 4], the pyrimido[6,1-b][1,3]thiazepin-7,9(8H)-diones are compounds which are novel in their skeleton itself and not described in the literature.

25 With respect to the thiazolo[3,2-c]pyrimidine-5,7(6H)-dione derivatives, for example, 6,8-diethyl-2-hydroxymethyl-2,3-dihydrothiazolo[3,2-c]pyrimidine-5,7(6H)-dione is reported as a metabolite of 1-allyl-3,5-diethyl-6-chlorouracil [R. Kaul et al., J. Pharm. Sci. 71, 897 (1982); Xenobiotica 12, 495 (1982); Arzneim-Forsch. 32, 610 (1982)]. However, there is no report of its systematic synthesis. Also, as to the pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione derivatives, for example, perhydropyrimido[6,1-b][1,3]thiazine-6,8-dione derivatives are reported in D. M. Brown et al., J. Chem. Soc., 2385 (1972). However, there is no report of the systematic synthesis of these derivatives.

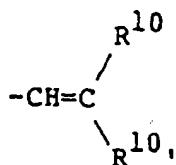
Also, no pharmacological actions of these derivatives are known at all.

30 With reference to the above-mentioned formula (1), the alkyl or alkenyl group (1) represented by R¹ may be an alkyl group of 1 to 8 carbon atoms such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, sec-butyl, pentyl, i-pentyl, hexyl, heptyl and octyl; or an alkenyl group of 2 to 8 carbon atoms such as vinyl, allyl, 1-propenyl, isopropenyl, 2-but enyl, 1,3-butadienyl, 2-pentenyl, 1-hexenyl, 1-heptenyl or 1-octenyl, either of which (alkyl or alkenyl) may be substituted. The substituents of the said alkyl or alkenyl group represented by R¹ are selected from cyano, carbamoyl, pyridyl, quinolyl, hydroxyl, lower (C₁ to C₄) alkoxy, amino, lower (C₁ to C₄) alkyl, carboxyl, lower (C₁ to C₄) alkoxy carbonyl and lower (C₂ to C₆) alkanoylamino groups. The aralkyl group (2) represented by R¹ is the group obtained by combining a phenyl or naphthyl group with an alkylene group of 1 to 4 carbon atoms, such as methylene, ethylene, trimethylene or tetramethylene. The phenyl or naphthyl group may be substituted by 1 to 3 halogen atoms (such as fluorine, chlorine or bromine), lower (C₁ to C₄) alkyl (such as methyl or ethyl), phenyl, o-cyano-phenyl, methoxy, ethoxy or nitro groups.

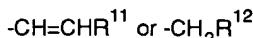
40 The phenyl or naphthyl group (3) represented by R¹ may be substituted by 1 to 3 halogen atoms (such as fluorine, chlorine or bromine), lower (C₁ to C₄) alkyl (such as methyl or ethyl), alkoxy (such as methoxy or ethoxy) or nitro groups.

The aliphatic hydrocarbon group (2) represented by R² has the formula:

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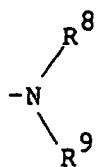


wherein R¹⁰ represents a cyano, carbamoyl or lower (C₁ to C₄) alkoxy carbonyl group; R¹² represents a lower (C₁ to C₈) alkyl, phenyl, naphthyl, cyano, carbamoyl or lower (C₁ to C₄) alkoxy carbonyl group; and R¹² represents a dimethylamino, diethylamino, morpholino, piperidino or piperazino group.

55 The phenyl or naphthyl group (3) represented by R² may be substituted by 1 to 3 halogen atoms (such as fluorine, chlorine or bromine), lower (C₁ to C₄) alkyl (such as methyl or ethyl), alkoxy (such as methoxy or ethoxy) or nitro groups.

The unsubstituted or substituted amino group (4) represented by R² is denoted by the formula:

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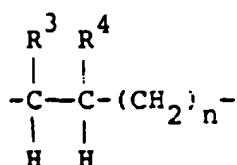


wherein each of R^8 and R^9 is hydrogen, a lower alkyl group having 1 to 8 carbon atoms (such as methyl, ethyl, propyl or butyl) or a fatty acid-derived acyl group having 1 to 8 carbon atoms (such as formyl, acetyl, propionyl or butyryl).

10 The halogeno group (7) represented by R^2 may be fluorine, chlorine, bromine or iodine.

The above-mentioned unsaturated or saturated divalent hydrocarbon chain of 2 to 4 carbon atoms represented by A may be a chain represented by the formula:

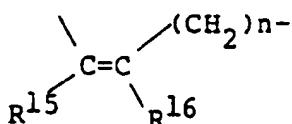
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20 wherein R^3 represents hydrogen, a lower (C_1 to C_4) alkyl group which may be substituted by an halogen atom, or a lower (C_1 to C_4) alkylthio or a phenylthio group (such as chloromethyl, alkylthiomethyl or phenylthiomethyl), or -YR^5 [wherein Y is -O- or -S- , and R^5 is hydrogen, a lower alkyl group of 1 to 4 carbon atoms (such as methyl or ethyl) or a phenyl or naphthyl group, which may be substituted by an alkyl group of 1 to 4 carbon atoms, or an alkoxy group of 1 to 4 carbon atoms or by phenyl, which may itself be substituted by one to three halogen atoms], or a fatty acid-derived lower acyl group of 1 to 4 carbon atoms (such as acetyl or trifluoroacetyl); R^4 represents hydrogen or a lower alkyl group of 1 to 4 carbon atoms (such as methyl or ethyl); and n represents an integer of 0 to 2.

25 The unsaturated or saturated divalent hydrocarbon chain of 2 to 4 carbon atoms represented by A may also be a chain represented by the formula:

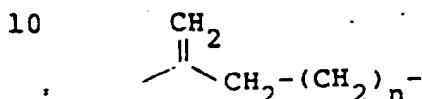
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35 wherein R^{15} and R^{16} represent hydrogen, a lower alkyl group of 1 to 4 carbon atoms (such as methyl or ethyl), -COOR^{17} wherein R^{17} is hydrogen or lower (C_1 to C_4) alkyl or -NHR^{18} wherein R^{18} is hydrogen, lower (C_1 to C_4) alkyl or lower (C_1 to C_4) alkanoyl; and n represents an integer of 0 to 2.

The unsaturated or saturated divalent hydrocarbon chain of 2 to 4 carbon atoms represented by A may further be a chain represented by the formula:

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45 wherein n represents an integer of 0 to 2.

In this specification, the word "lower" before an alkyl moiety designates 1-4 carbon atoms.

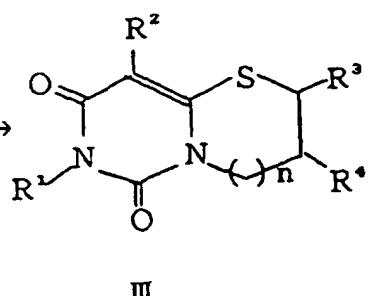
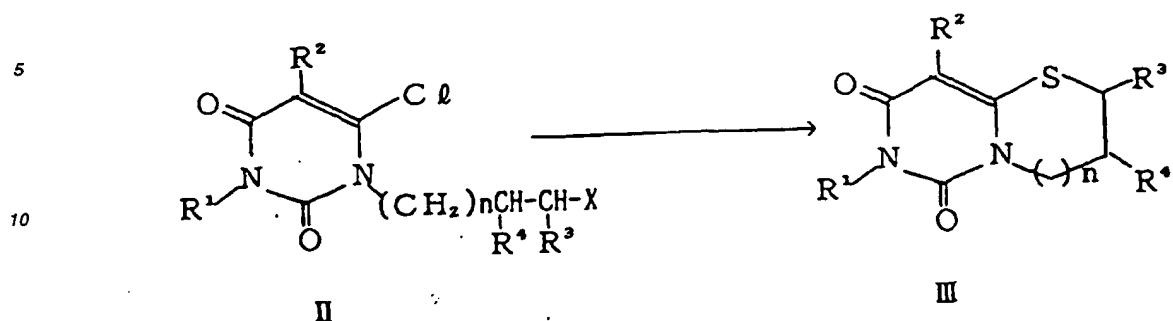
Of the above-mentioned compounds represented by formula (I), the compounds in which R^1 is an alkyl group of 3 to 8 carbon atoms or an aralkyl group which may be substituted, R^2 is an aryl group which may be substituted, and A is a divalent hydrocarbon chain of 2 to 3 carbon atoms are particularly preferred.

50 The salts of the compounds represented by formula (I) include pharmacologically acceptable salts, for example, acid-addition salts, namely inorganic salts, such as hydrochlorides, hydrobromides, sulfates, nitrates and phosphates, and organic salts such as acetates, tartrates, citrates, fumarates and maleates.

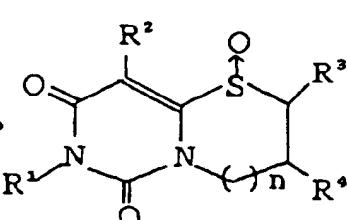
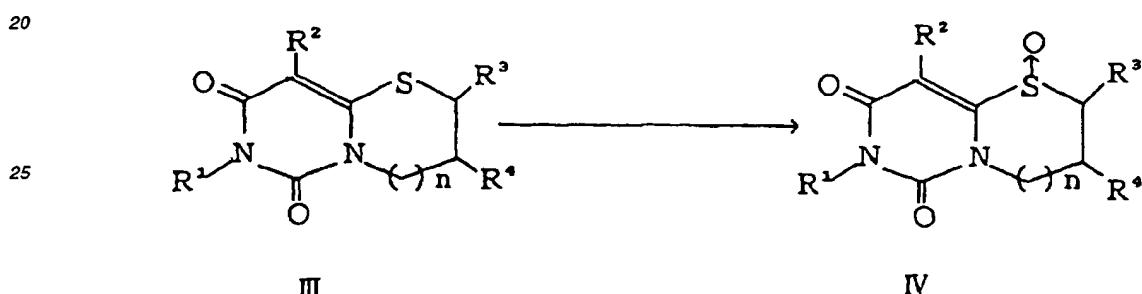
Manufacturing Method

55 The compounds represented by formula (I) can be produced by the following methods.

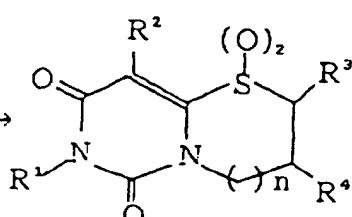
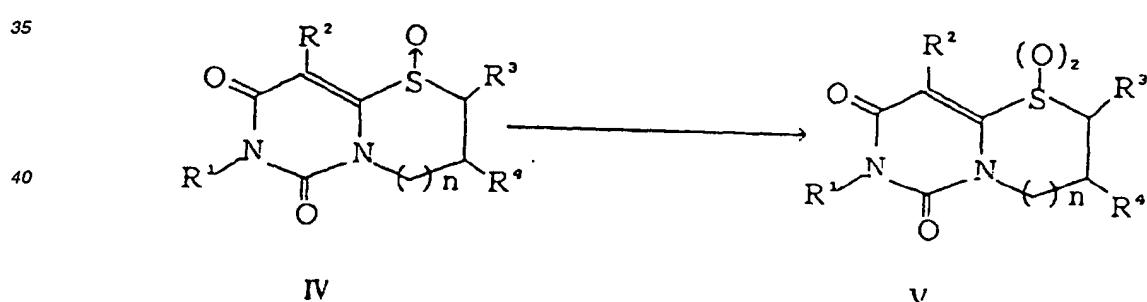
Reaction (a):



Reaction (b):



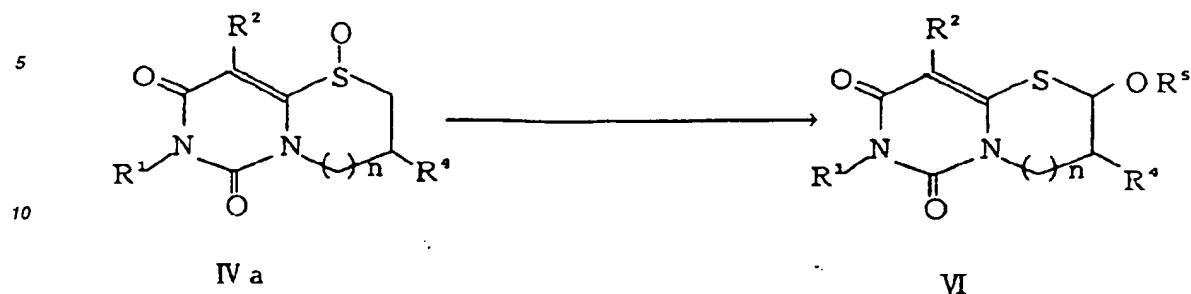
Reaction (c):



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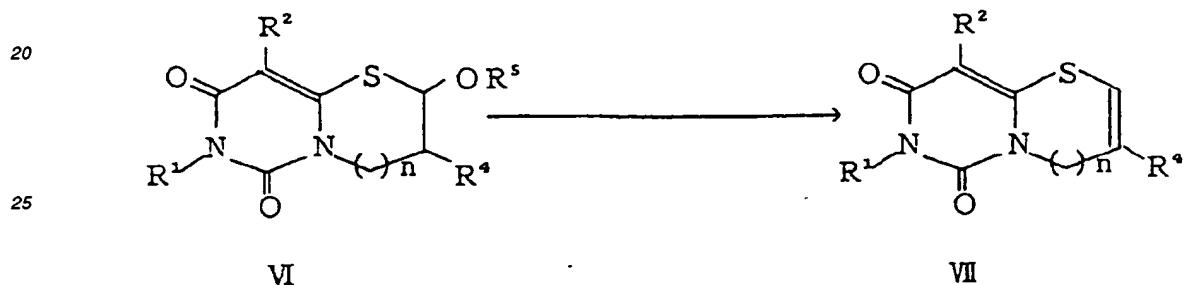
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Reaction (d):



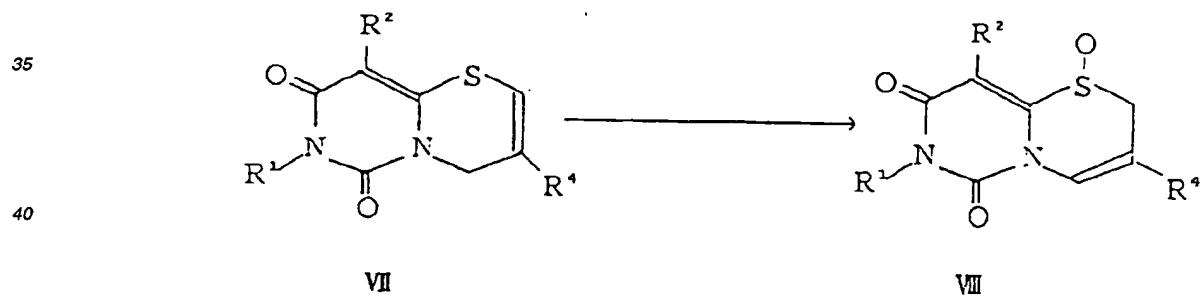
wherein R¹, R², R⁴, R⁵ and n have the same meanings as given above.

Reaction (e):



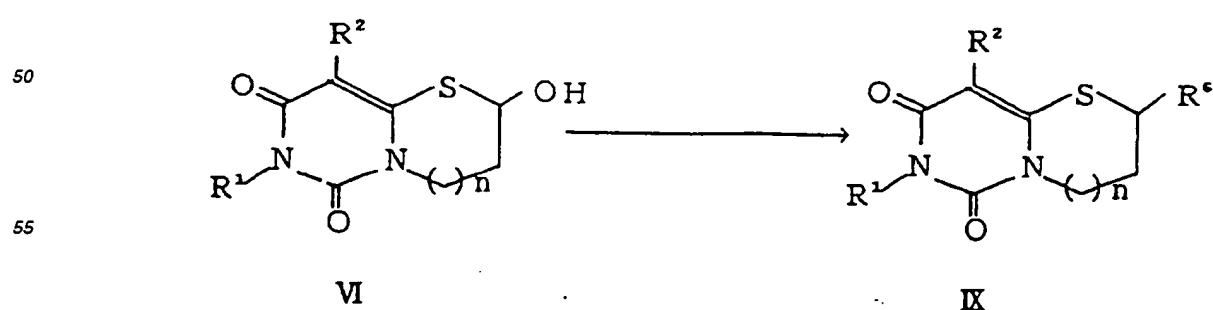
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Reaction (f):



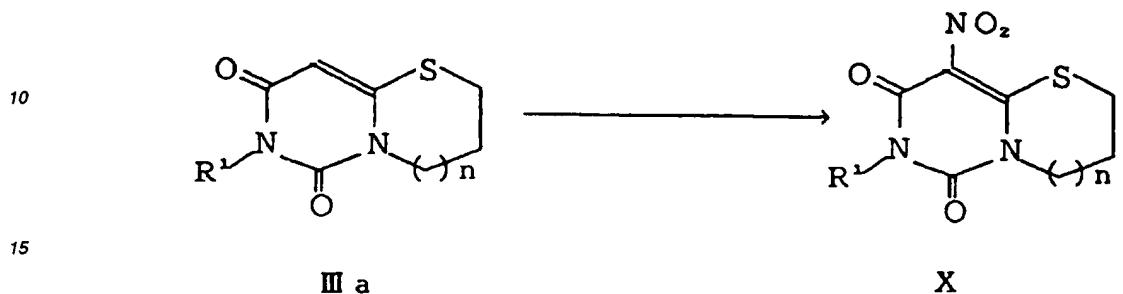
wherein R¹, R² and R⁴ have the same meanings as given above.

Reaction (g):



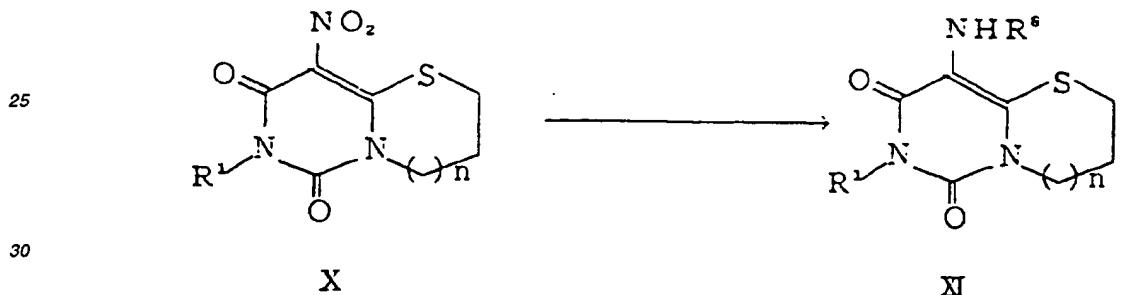
wherein R¹, R² and n have the same meanings as given above; and R⁶ represents an alkylthio group having about 1 to 4 carbon atoms, an alkoxy group having about 1 to 4 carbon atoms, or an arylthio or aryloxy group which may be substituted.

5 Reaction (h):



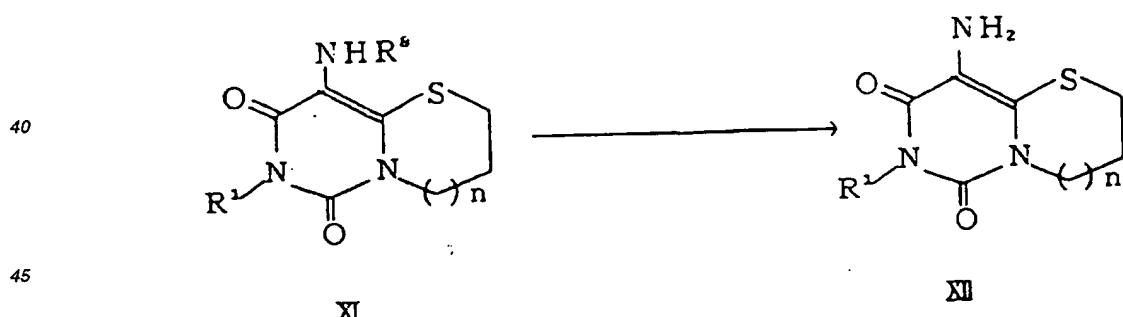
wherein R¹ and n have the same meanings as given above.

20 Reaction (i):



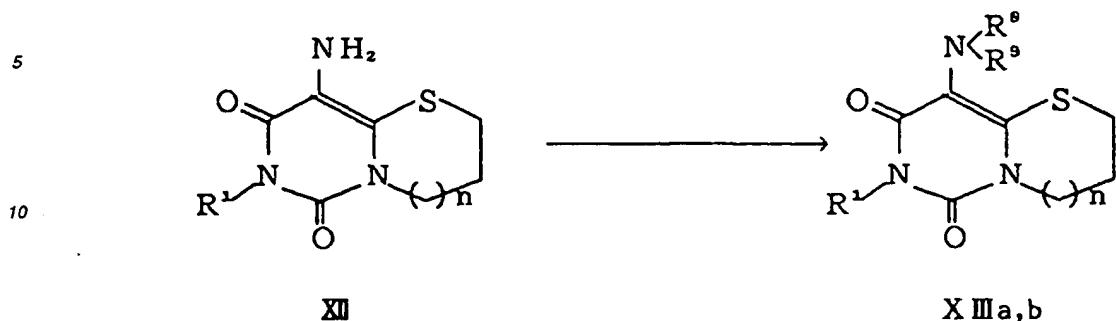
wherein R¹, R⁶ and n have the same meanings as given above.

35 Reaction (j):

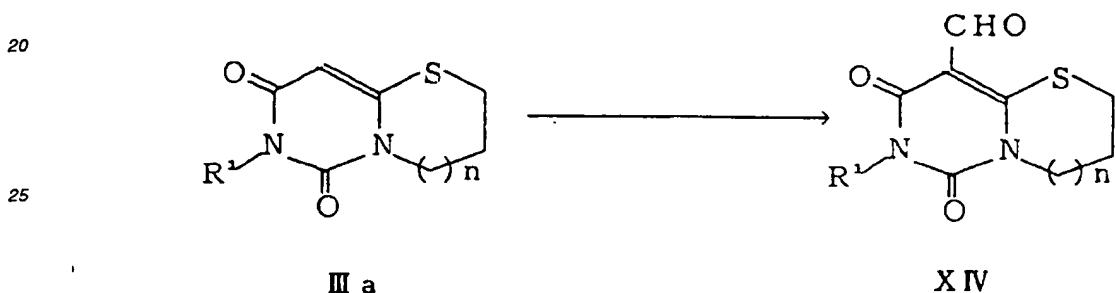


wherein R¹, R⁶ and n have the same meanings as given above.

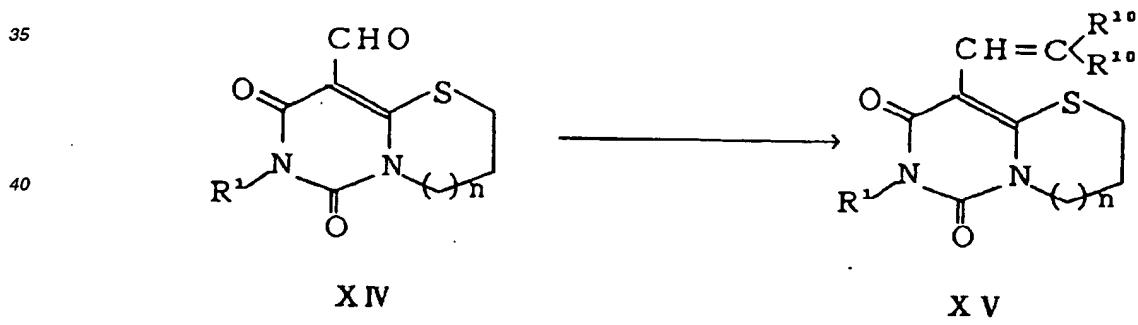
Reaction (k):



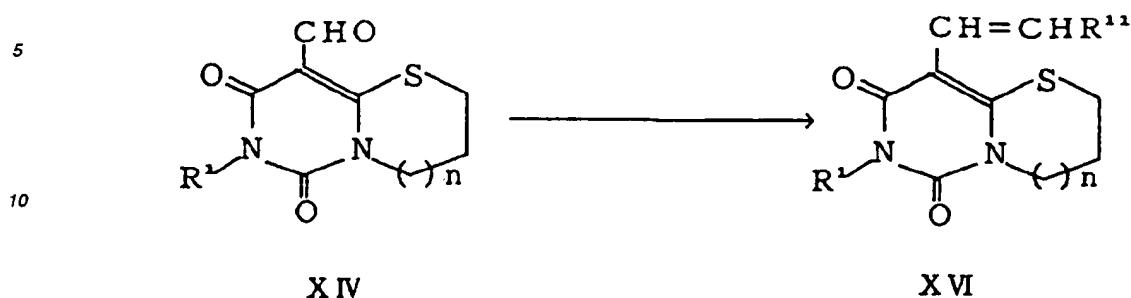
Reaction (l):



Reaction (m):



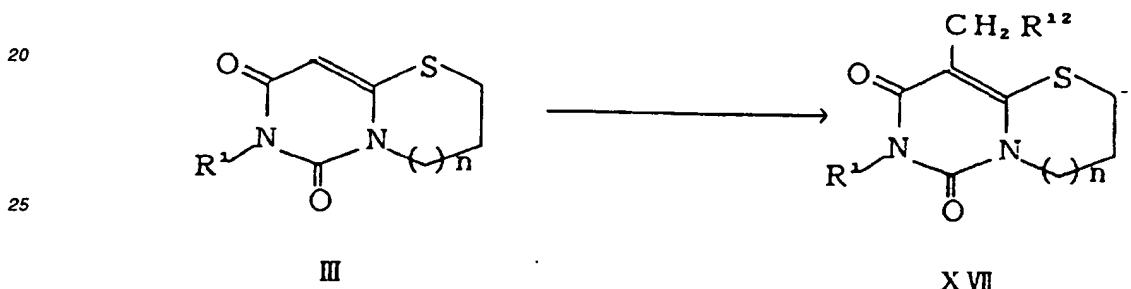
Reaction (n):



wherein R¹, R¹¹ and n have the same meanings as given above.

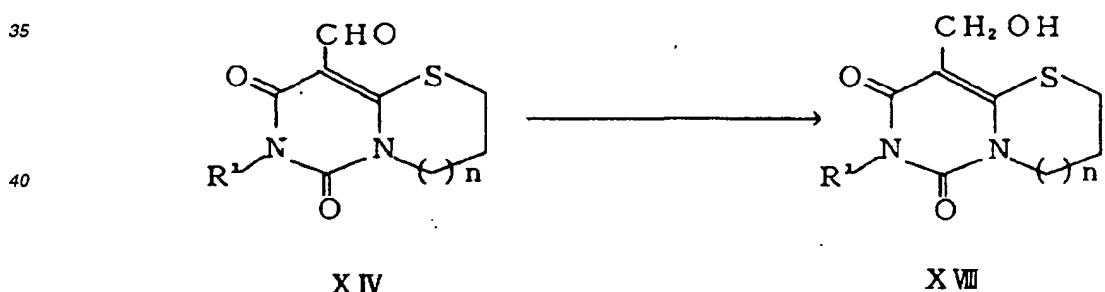
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Reaction (o):



30 wherein R¹, R¹² and n have the same meanings as given above.

Reaction (p):

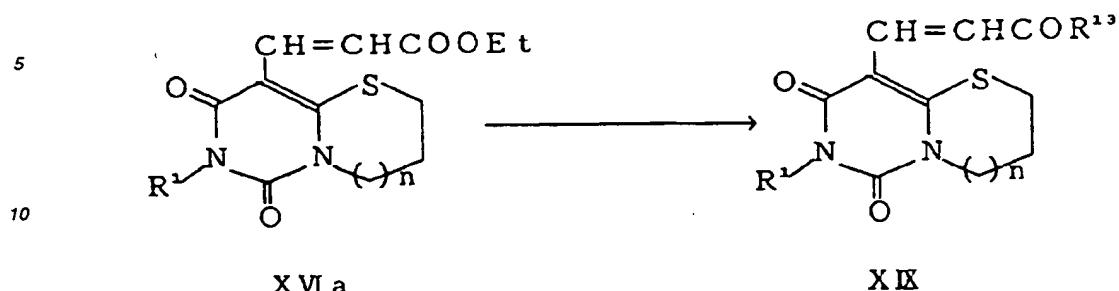


wherein R¹ and n have the same meanings as given above.

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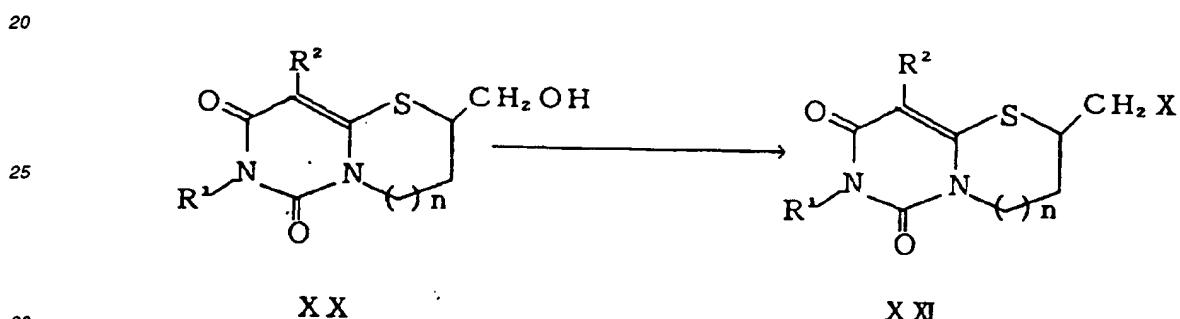
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Reaction (q):



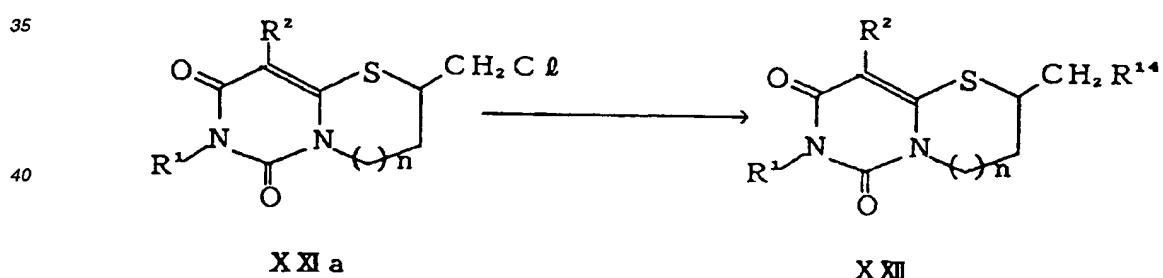
15 wherein R¹ and n have the same meanings as given above; R¹³ represents a secondary amino group substituted by an alkyl group of 1 to 5 carbon atoms which may be substituted; and the substituent alkyl group may combine to form a cyclic group (such as piperidino, morpholino, piperazino or N'-phenylpiperazino).

Reaction (r):



30 wherein R¹, R² and n have the same meanings as given above; and X represents chlorine.

Reaction (s):

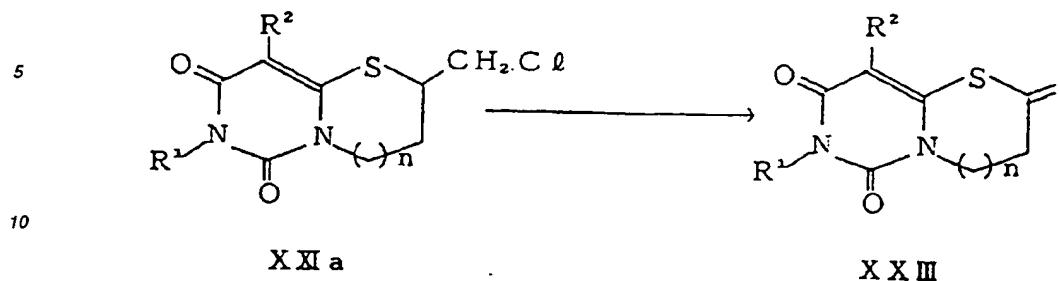


45 wherein R¹, R² and n have the same meanings as given above; and R¹⁴ represents an alkylthio group having about 1 to 4 carbon atoms or an arylthio group which may be substituted (such as alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or phenylthio which may be substituted by one or more halogen atoms).

50

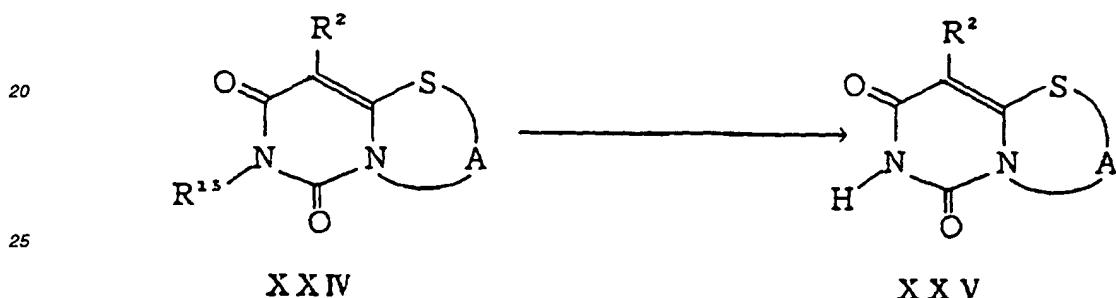
55

Reaction (t):



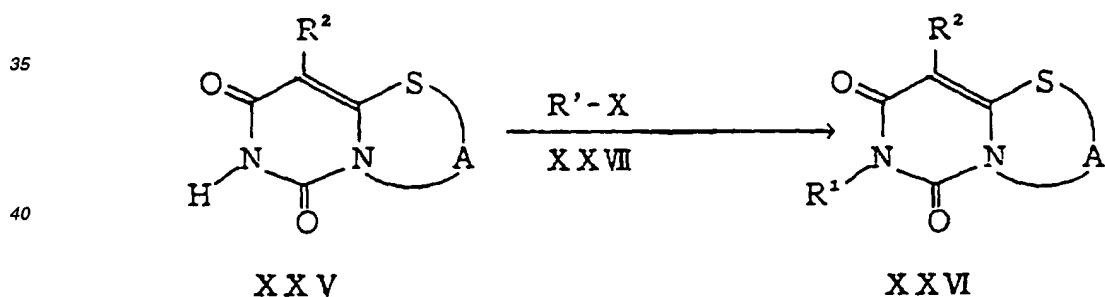
wherein R¹, R² and n have the same meanings as given above.

15 Reaction (u):



wherein R² and A have the same meanings as given above. R⁵ represents a benzyl group which may be substituted.

30 Reaction (v):



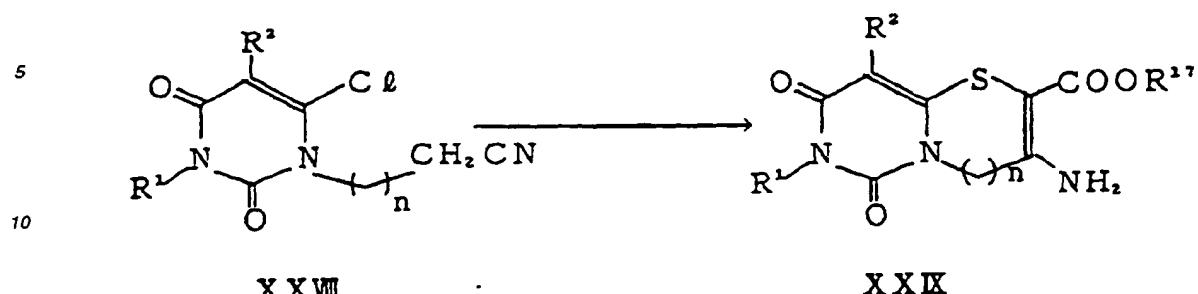
wherein R¹, R² and A have the same meanings as given above.

45

50

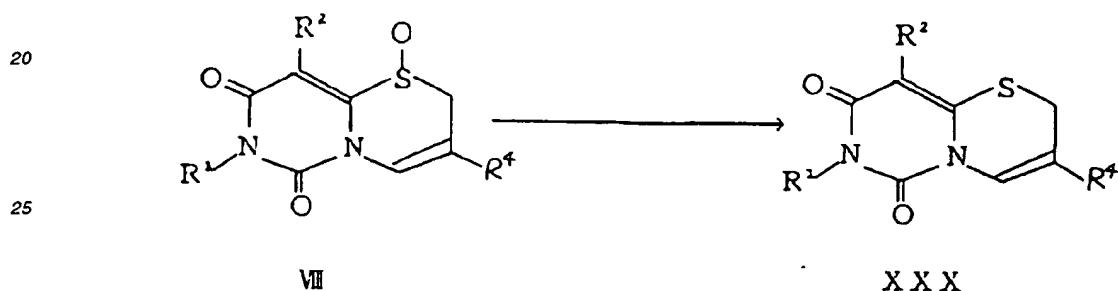
55

Reaction (w):



wherein R¹, R², R¹⁷, A and n have the same meanings as given above.

Reaction (x):



wherein R¹, R² and R⁴ have the same meanings as given above.

In the above-mentioned reaction (a), compound (II) is reacted with a sulfur reagent in an organic solvent to obtain compound (III).

As such organic solvents, there can be used aprotic solvents including carboxylic acid amides such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethyl sulfoxide; ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; and other solvents such as acetonitrile, ethylene glycol dimethyl ether, tetrahydrofuran and dioxane. In particular, the carboxylic acid amides and sulfoxides are preferably used.

Such sulfur reagents include sodium hydrosulfide (NaSH), sodium sulfide (Na_2S) and ammonium sulfide ($(\text{NH}_4)_2\text{S}$). Sodium hydrosulfide is preferably used. Such a reagent is preferably used in an amount 2 to 4 times that of compound (II).

Further, this reaction is usually conducted at temperatures of 0-30°C for 0.5 to 10 hours. It is preferable to add sodium hydrosulfide to a solution of compound (II) in N,N-dimethylformamide under ice cooling, followed by stirring at room temperature for about 1 to 2 hours.

In reaction (b), compound (III) is reacted with an oxidizing agent in an organic solvent to obtain compound (IV).

As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxan; and ketones such as acetone and methyl ethyl ketone. In particular, the halogenated hydrocarbons are preferably used.

Such oxidizing agents include organic peracids such as m-chloroperbenzoic acid; N-halocarboxylic acid amide such as N-bromosuccinic acid amide; and periodic acid. In particular, m-chloroperbenzoic acid is preferably used. Such a compound is preferably used in an amount slightly more than one equivalent in relation to compound (III).

50 Further, it is preferable that this reaction is conducted by adding m-chloroperbenzoic acid to a solution of compound (III) in methylene chloride little by little with stirring under ice cooling, followed by stirring at temperatures of 0-30°C for about 3 to 10 hours.

In reaction (c), compound (IV) is reacted with an oxidizing agent in an organic solvent to obtain compound (V).

As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxan; and ketones such as acetone and methyl ethyl ketone. In particular, the halogenated hydrocarbons are preferably used.

Such oxidizing agents include organic peracids such as m-chloroperbenzoic acid; N-halocarboxylic acid amide such as N-bromosuccinic acid amide; and periodic acid. In particular, m-chloroperbenzoic acid is preferably used. Such

a compound is preferably used in an amount slightly more than one equivalent of compound (IV).

Further, it is preferable that this reaction is conducted by adding m-chloroperbenzoic acid to a solution of compound (IV) in methylene chloride little by little with stirring under ice cooling, followed by stirring at temperatures of 0-30°C for about 5 to 20 hours.

5 In reaction (d), compound (IVa) is reacted with an acid anhydride in an organic solvent to obtain compound (VI).

As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxan; and ketones such as acetone and methyl ethyl ketone. The acid anhydrides used in the reaction can also be employed as solvents. In particular, the halogenated hydrocarbons such as dichloromethane and dichloroethane are preferably used.

10 Such acid anhydrides include acetic anhydride and trifluoroacetic anhydride can be used depending on their purpose. Such an acid anhydride is used in an amount usually 1 to 10 times, preferably 2 to 3 times that of compound (IVa). Further, this reaction is usually conducted at temperatures of 0-30°C for 5 to 30 hours. It is preferable to add the acid anhydride to a solution of compound (IVa) in dichloroethane, followed by stirring at room temperature for about 10 to 20 hours.

15 The reaction product thus obtained is a 2-O-acyl form in which R⁵ is an acyl group such as acetyl and trifluoroacetyl. When an amine (for example, triethylamine) is allowed to exist in the reaction solution in an amount about 1 to 2 times that of the acid anhydride, a 2-hydroxy form in which R⁵ is a hydrogen atom can be obtained. In this case, it is preferred that the reaction conditions are similar to those under which the 2-O-acyl form is obtained, except that the amine is used.

20 In reaction (e), compound (VI) is reacted in an organic solvent in the presence of an acid catalyst to obtain compound (VII).

As such organic solvents, there can be used aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxan; and ketones and nitriles usually used as solvents. In particular, the aromatic hydrocarbons such as benzene and toluene are preferably used.

25 Such acid catalysts include sulfonic acids such as methanesulfonic acid, p-toluenesulfonic acid and trifluoromethanesulfonic acid; and other catalysts such as trichloroacetic acid and sulfuric acid. In particular, the sulfonic acids such as p-toluenesulfonic acid are preferably used. It is preferred that such an acid catalyst is used in a catalytic amount.

Further, this reaction is usually conducted at a temperature from room temperature up to the boiling point of the solvent used for about 3 to 30 hours. It is preferable to add a catalytic amount of p-toluenesulfonic acid to a solution of compound (VI) in toluene, followed by heating under reflux for about 4 to 7 hours.

30 Alternatively, compound (VII) may be obtained easily by conducting reactions (b), (d) and (e) serially under similar conditions as described above, without isolation of the reaction products (IV) and (VI).

In reaction (f), compound (VII) is reacted with an oxidizing agent in an organic solvent to obtain compound (VIII).

As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxane; and ketones such as acetone and methyl ethyl ketone. In particular, the halogenated hydrocarbons are preferably used.

Such oxidizing agents include peracids such as m-chloroperbenzoic acid; N-halocarboxylic acid amide such as N-bromosuccinic acid amide; and periodic acid. In particular, m-chloroperbenzoic acid is preferably used. Such a compound is preferably used in an amount slightly more than one equivalent of compound (VII).

40 Further, it is preferable that this reaction is conducted by adding m-chloroperbenzoic acid to a solution of compound (VII) in methylene chloride little by little with stirring under ice cooling, followed by stirring at temperatures of 0-30°C for about 3 to 10 hours.

In reaction (g), compound (VI) is reacted with a nucleophilic reagent in an organic solvent in the presence of an acid catalyst to obtain compound (IX).

45 As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; and ethers such as tetrahydrofuran and dioxane. When alcohols such as methanol and ethanol or mercaptans are used as nucleophilic reagents, these compounds themselves can be used as solvents. In particular, the halogenated hydrocarbons such as dichloroethane are preferably used.

50 As such acid catalysts, there can be used organic acids such as acetic acid, trichloroacetic acid and p-toluenesulfonic acid; and inorganic acids such as hydrogen chloride, sulfuric acid and boron trifluoride. The catalyst used for the reaction can be suitably changed depending on the nucleophilic reagent used.

The nucleophilic reagents include alcohols such as methanol and ethanol, and thiols such as ethyl mercaptan and thiophenol. Such a compound is used in an amount equivalent to compound (VI) or in large excess (when used as the solvent). However, the thiol is preferably used in an amount about 2 to 5 times that of compound (VI). Further, this reaction is conducted at temperatures of 0-50°C for about 10 hours to 3 days, preferably at room temperature for about 1 to 3 days.

55 In reaction (h), compound (IIIa) is reacted with a nitrating agent in a solvent to obtain compound (X).

Such a solvent is suitably changed depending on the nitrating agent used for the reaction.

The nitrating agents include various reagents, for example, so-called mixed acid prepared by combining nitric acid and sulfuric acid, acetyl nitrate, nitric acid, nitronium tetrafluoroborate ($\text{NO}_2^+\text{BF}_4^-$), nitrogen oxides (NaNO_2 and N_2O_5) and ethyl nitrate. Of these reagents, mixed acid is more preferable as the sure, inexpensive nitrating agent. When mixed acid is used as the nitrating agent, it is preferred to use the reagent itself as the solvent. Such a nitrating agent is used usually in large excess, preferably in an amount about 3 to 10 times that of compound (IIIa).

Further, this reaction is usually conducted at temperatures of 0-30°C for 0.5 to 3 hours. It is preferable to add fuming nitric acid to a solution of compound (IIIa) in concentrated sulfuric acid little by little under ice cooling so as to keep a reaction temperature at about 0 to 5°C, followed by stirring at a similar temperature for about 0.5 to 2 hours.

In reaction (i), the nitro group of compound (X) is reduced to an amino group by a reducing agent, and the resulting amino derivatives allowed to react with an organic carboxylic acid or an anhydride thereof, thereby obtaining compound (XI).

Such an organic solvent is suitable selected depending on the reducing agent used at that time.

The reducing agents include catalytic reducing agents which react in the presence of a palladium catalyst or the like, sulfur reducing agents such as sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_4$) and metals such as iron and zinc. In particular, when iron or zinc is used as the reducing agent, an alcohol such as methanol or ethanol used as the organic solvent may contain a suitable amount of an organic acid such as formic acid or acetic acid. The organic acid reacts with the amino group produced by reduction of the nitro group to form an acylamino derivative (X). In this case, the use of an organic acid as the solvent is more convenient and preferable.

Further, this reaction is usually conducted at a temperature around the boiling point of the solvent for about 3 to 20 hours. It is preferable to react compound (X) in the organic acid such as acetic acid for about 3 to 5 hours while heating under reflux in the presence of zinc in an amount of 3 to 5 times that of compound (X).

In reaction (j), compound (XI) is hydrolyzed in an organic solvent in the presence of an acid to obtain compound (XII).

Such organic solvents include alcohols such as methanol and ethanol, and ethers such as tetrahydrofuran and dioxane. In particular, the alcohols such as methanol and ethanol are preferably used.

As such acids, mineral acids such as hydrochloric acid and sulfuric acid are preferably used.

Further, this reaction is usually conducted at a boiling point of the solvent for about 2 to 10 hours. It is preferable to add a one-fifth to equivalent amount of 0.5 to 2 N-hydrochloric acid in relation to compound (XI) to an alcoholic solution of compound (XI) to conduct the reaction for about 2 to 5 hours.

In reaction (k), compound (XII) is alkylated by an alkylating agent in an organic solvent to obtain an alkylamino form (XIIIa), and acylated by an acylating agent in an organic solvent to obtain an acylamino form (XIIIb).

In alkylation reaction, as such organic solvents, there can be used aprotic solvents usually employed, including carboxylic acid amides such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethyl sulfoxide; ketones such as acetone and methyl ethyl ketone; and other solvents such as acetonitrile.

In particular, the carboxylic acid amides and sulfoxides are preferably used.

In reaction (l), compound (IIIa) is reacted with a formylating agent in an organic solvent to obtain compound (XIV).

Such an organic solvent varies depending on what compound is used as the formylating agent. The organic solvents include alcohols, ketones, halogenated hydrocarbons, ethers, esters, amides and sulfoxides which are usually used as solvents, but are not limited thereto.

Such formylating agents include Vilsmeier reagents (N,N-dimethylformamide-phosphorus oxychloride), acid anhydrides (formic acetic anhydride), ethyl formate-sodium ethoxide, chloroform-potassium hydroxide (Reimer-Tiemann reaction) and chloral ($\text{Cl}_3\text{C}-\text{CHO}$). In particular, the Vilsmeier reagents are preferably used. Such a formylating agent is preferably used in an amount more than one equivalent in relation to compound (IIIa). The Vilsmeier reagents (N,N-dimethylformamide-phosphorus oxychloride) are preferably used in an amount of 1.5 to 3 equivalents.

Further, it is preferable that this reaction is conducted by adding the Vilsmeier reagent previously prepared to a solution of compound (IIIa) in N,N-dimethylformamide little by little with stirring under ice cooling so that the reaction temperature does not exceed about 40°C, followed by stirring at room temperature for about 2 to 5 hours.

In reaction (m), compound (XIV) is condensed with an active methylene compound in a solvent in the presence of a base to obtain compound (XV).

Such organic solvents include alcohols such as methanol and ethanol; ethers such as tetrahydrofuran and dioxane; and carboxylic acid amides such as dimethylformamide.

Further, such bases include potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride and potassium t-butoxide.

Furthermore, such active methylene compounds include malonitrile, malonic esters and malonic acid amide.

It is preferable that the solvent and the base used for the reaction is suitably selected depending on the active methylene compound reacted at that time.

Moreover, this reaction is usually conducted at a temperature of about 50°C to the boiling point of the solvent for about 5 to 20 hours.

In reaction (n), compound (XIV) is reacted with a Wittig reagent in an organic solvent to obtain compound (XVI).

Such organic solvents include halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene and toluene; and alcohols such as methanol and ethanol.

5 Further, such Wittig reagents include stabilized phosphoranes, semi-stabilized phosphoranes and unstabilized phosphoranes such as carboethoxymethylenetriphenylphosphorane, cyanomethylenetriphenylphosphorane, pentylmethylenetriphenylphosphorane and benzylidenetriphenylphosphorane.

Furthermore, this reaction is usually conducted at a temperature of about 50°C to the boiling point of the solvent for about 5 to 20 hours. It is preferable to heat compound (XIV) and the Wittig reagent under reflux in an appropriate solvent for about 5 to 10 hours.

10 In reaction (o), compound (III) is aminomethylated by the reaction of formaldehyde and an amine, namely the Mannich reaction to obtain compound (XVII).

Such organic solvents include alcohols such as methanol and ethanol; ethers such as tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloroethane, carbon tetrachloride and chloroform; and other usual solvents such as 15 acetonitrile and acetic acid.

As Mannich reagents, there can be used appropriate combinations of paraformaldehyde or formic acid with secondary amines (for example, dimethylamine hydrochloride, diethylamine hydrochloride, piperidine, morpholine, piperazine and salts thereof. Such a compound is preferably used in an amount 2 to 5 times that of compound (III)).

Further, it is preferable that this reaction is usually conducted by heating compound (III) and the Mannich reagent 20 in the suitable solvent at a temperature around the boiling point of the solvent for about 10 to 20 hours.

In reaction (p), compound (XIV) is reacted with a reducing agent in a solvent.

Such organic solvents include alcohols such as methanol and ethanol; and ethers such as ethyl ether, tetrahydrofuran and dioxane.

Such reducing agent include metal hydride complex compounds such as sodium borohydride and aluminium lithium 25 hydride, and tributyltin hydrides and are preferably used in an amount 2 to 4 times that of compound (XIV).

It is preferable that the reaction is conducted at temperatures of 0°-30°C for 0.5 to 2 hours after addition of sodium borohydride to a solution of the compound (XIV) in alcohol.

In reaction (q), compound (XVIa) is reacted in an aprotic solvent with a dimethylaluminum amide derivative obtained by reacting a primary or secondary amine with trimethylaluminium according to the method described in the literature 30 [A. Basha S, *Tetrahedron Lett.* **48**, 4171 (1977)].

As such aprotic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; and ethers such as ethyl ether, tetrahydrofuran and dioxane. In particular, halogenated hydrocarbons such as dichloromethane and dichloroethane are preferably used.

The synthesis of the dimethylamide is conducted by adding a solution of trimethylaluminium in hexane to the amine 35 (for examples an alkyl amine, an aryl amine, morpholine, piperidine and N-phenylpiperazine) in the solvent such as methylene chloride, chloroform or dichloroethane in a stream of nitrogen to form the dimethylaluminum amide form.

It is preferable that this reaction is usually conducted by adding a solution of compound (XVIa) in the same solvent as used in the preparation of the dimethylaluminum amide form, such as methylene chloride, little by little with stirring at temperatures of 0-30°C, and then heating the mixture under reflux for about 10 to 30 hours.

40 After the reaction is completed, the unreacted aluminum reagent is decomposed with hydrochloric acid, and then the reaction product thus obtained can be easily isolated and purified by methods known in the art.

In reaction (r), compound (XX) is reacted with a halogenating reagent in an organic solvent to obtain compound (XXI).

45 As such organic solvents, there are preferably used aprotic solvents including halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; and ethers such as ethyl ether, tetrahydrofuran and dioxane.

Further, as such halogenating reagents, there can be used thionyl chloride, phosphorus oxychloride, phosphorus trichloride and phosphorus pentachloride. In particular, thionyl chloride is preferably used because of easy treatments after the reaction. As to this reaction, it is preferable to add the halogenating reagent such as thionyl chloride to a solution of compound (XX) in dichloromethane or dichloroethane little by little at temperatures of 0°C-30°C, followed 50 by heating under reflux for about 5 to 20 hours.

In reaction (s), compound (XXIa) is reacted with a nucleophilic reagent in an organic solvent to obtain compound (XXII).

55 As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol and methyl cellosolve; and carboxylic acid amides such as dimethyl-formamide. It is preferable that the solvent used is suitably selected depending on the nucleophilic reagent used.

Such nucleophilic reagents include thiols such as thiophenols and methyl mercaptan; alcohols such as methanol and ethanol; and amines such as alkyl amines, aralkyl amines and aromatic amines.

This reaction is preferably conducted in the presence of an appropriate base such as potassium carbonate, sodium carbonate or sodium hydride.

With respect to this reaction, it is preferred to react compound (XXIa) in the solvent such as ethanol in the presence of the base such as potassium carbonate at a temperature from room temperature up to the boiling point of the solvent for about 5 to 50 hours.

In reaction (t), compound (XXIa) is reacted with a base in an organic solvent to obtain compound (XXIII).

As such organic solvents, there can be used halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; ethers such as ethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol and ethanol; carboxylic acid amides such as dimethyl-formamide; and amines such as pyridine.

As such bases, there can be used amines such as triethylamine, pyridine and piperidine; and alkali salts such as potassium t-butoxide, sodium hydride, potassium carbonate and sodium carbonate. It is preferable that the base is suitably selected depending on the solvent used.

Further, it is preferable that this reaction is usually conducted at temperatures of room temperature up to the boiling point of the solvent for about 5 to 50 hours.

After the reaction is completed, the reaction product thus obtained can be easily isolated and purified by recrystallization and column chromatography.

In reaction (u), compound (XXIV) is reacted with a debenzylating agent in an organic solvent to obtain compound (XXV).

As such organic solvents, there can be used aromatic hydrocarbons such as benzene, toluene and xylene; and halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane. In particular, benzene, toluene and xylene are preferable.

As such debenzylating agents, there can be used boron tribromide, metal sodium-liq. ammonia and catalytic reduction, among them BBr_3 is preferable for its simplicity. Such compounds may be added in an amount of about 2 to 10 moles, preferably 2 to 5 moles to 1 mole of compound (XXIV).

Further, it is preferable that this reaction is usually conducted by adding BBr_3 to a suspension of the compound (XXIV) in toluene at a temperature from 50°C up to the boiling point of the solvent for about 5 to 40 hours, preferably around the boiling point of the solvent for 10 to 20 hours.

In reaction (v), compound (XXV) is reacted with an alkylating agent (XXVII) in an organic solvent in the presence of base to obtain compound (XXVI).

As such organic solvents, there can be used dimethyl-formamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, acetone and ethylmethylketone.

As such bases, there can be used sodium hydride, potassium t-butoxide, potassium carbonate and sodium carbonate.

As such alkylating agents (XXVII), there can be used substituted halides such as chloride, bromide and iodide.

Further, it is preferable that this reaction is usually conducted by employing about 1 to 3 moles of potassium carbonate and about 1 to 3 moles of alkylating agent (XXVII) to 1 mole of compound (XXV) in dimethylformamide at a temperature from room temperature up to the boiling point of the solvent for about 5 to 40 hours, preferably around 50 to 100°C for 10 to 20 hours.

In reaction (w), compound (XXVIII) is reacted with thioglycolate in an organic solvent in the presence of base to obtain compound (XXIX).

As such organic solvents, there can be used alcohols such as methanol, ethanol and propanol; and amides such as dimethylformamide and dimethylacetamide.

As such bases, there can be used potassium carbonate, sodium carbonate, sodium hydride and potassium t-butoxide.

Further, it is preferable that this reaction is usually conducted by employing about 2 to 4 moles of thioglycolate and about 2 to 4 moles of potassium carbonate per 1 mole of compound (XXVIII) in ethanol at a temperature around the boiling point of the solvent for about 10 to 20 hours.

In reaction (x), compound (VIII) is reacted with a reducing agent in an organic solvent to obtain compound (XXX).

Such reducing agents include metal hydride complex compounds such as sodium borohydride and aluminium lithium hydride; halogenated phosphorous compounds like phosphorus trichloride; titanium trichloride and silicon trichloride, and phosphorus trichloride is preferable for its simplicity. As solvents, there can be used amides such as dimethylformamide and dimethylacetamide; and halogenated hydrocarbons such as dichloroethane and chloroform, and among them dimethylformamide is preferable.

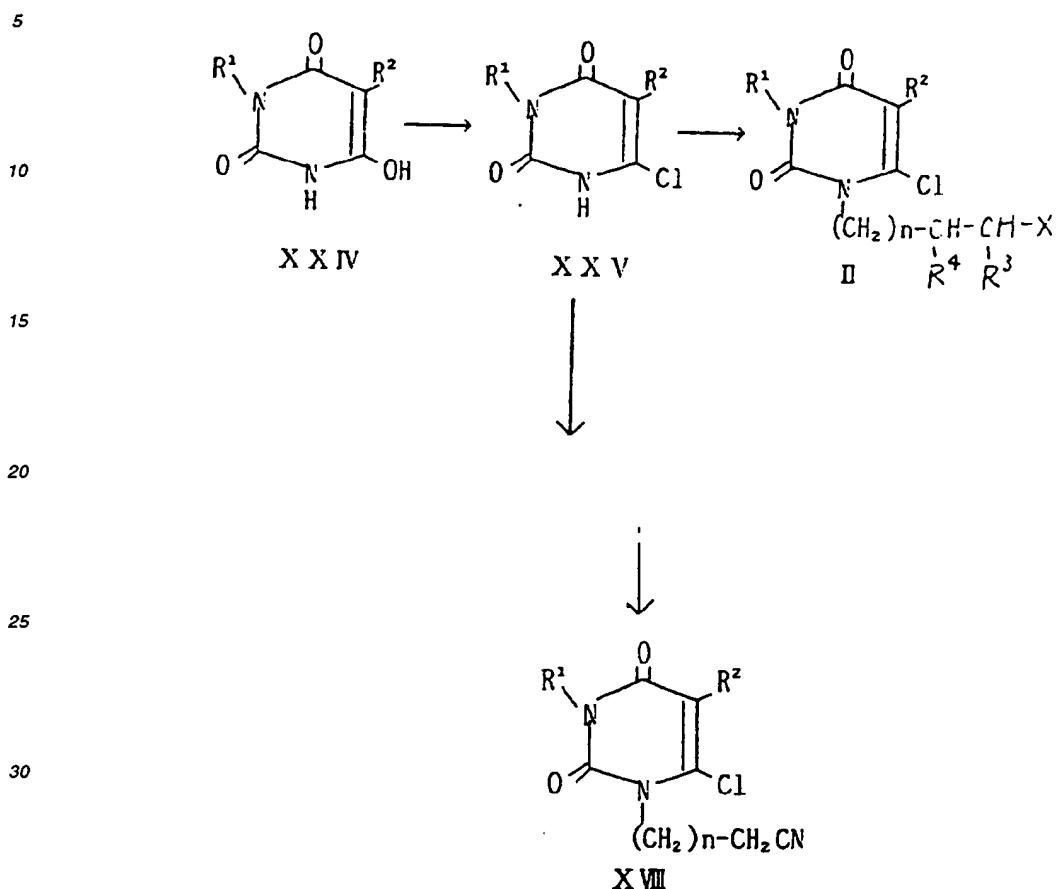
Further, it is preferable that this reaction is usually conducted by adding about 2 to 5 moles of phosphorus trichloride to 1 mole of compound (VIII) in DMF and mixing at a temperature from about -20°C to room temperature for about 30 minutes to 1 hour.

After the reaction is completed, the reaction product thus obtained can be easily isolated and purified by conventional methods such as column chromatography and recrystallization.

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In reactions (a) to (x), the starting compounds (II) and (XVIII) can be prepared by the following method.

Reaction (y):



(wherein each symbol has the same meaning as above given)

The starting compounds (II) can be easily obtained by reacting the compounds (XXV) synthesized by or in accordance with the methods described in *Chem. Ber.* **95**, 1597 (1962) and *Ann. Chem.* **691**, 142 (1966) with various alkyl dihalides (such as 1-bromo-2-chloroethane, 1-bromo-3-chloropropane, 1-bromo-4-chlorobutane and 1-bromo-3-chloro-2-methylpropane) in an aprotic solvent such as dimethylformamide in the presence of potassium carbonate or sodium carbonate at a temperature of 50 to 100°C for about 10 to 20 hours.

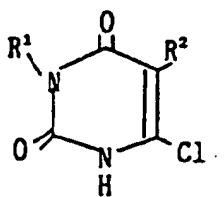
Reference Example 1

6-Chloro-5-phenyl-3-propylpyrimidine-2,4(1H,3H)-dione

Phosphorus oxychloride (500 ml) was added dropwise to 50% ethanol (100 ml) with stirring at room temperature. 5-Phenyl-3-propylpyrimidine-2,4,6(1H,3H)-trione (107 g) was added to the solution little by little with stirring. The reaction solution was heated at 50°C for 30 minutes, followed by heating under reflux for 4 hours. The reaction solution was concentrated under reduced pressure to dryness. The resulting syrup was poured on ice water little by little, and stirred for a while. The precipitated crystals were collected by filtration, washed with water, and then dried. Recrystallization from DMF (500 ml)-water (100 ml) gave colorless plates (73 g, 63%), m.p. 230 - 231°C.

Reference Examples 2 - 7

The following compounds were synthesized by methods similar to that of Reference Example 1.



10

Reference Example No.	R¹	R²	Yield (%)	Melting Point (°C)
2	Me	Ph	45	295-300
3	Et	Ph	71	220-223
4	Pr	H	71	196-200
15	Bu	Ph	75	205-208
5	Ph	Ph	44	> 300
6	Bzl	Ph	66	271-280
7				

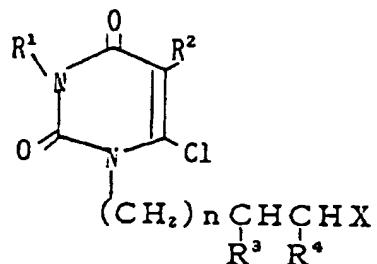
20 Reference Example 8

6-Chloro-1-(2-chloroethyl)-5-phenyl-3-propylpyrimidine-2,4(1H,3H)-dione

25 1-Bromo-2-chloroethane (3 ml) and potassium carbonate (3.48g) were added to a solution of 6-chloro-5-phenyl-3-propylpyrimidine-2,4(1H,3H)-dione (4 g) in DMF (40 ml), and the mixture was stirred at 50°C for 20 hours. The reaction solution was concentrated to dryness. A resulting residue was dissolved in chloroform and H₂O, and the organic layer was washed with water and dried. The solvent was evaporated to dryness to give a syrup, which was purified by column chromatography on silica gel.

30 Reference Examples 9 to 42

The following compounds were synthesized by methods similar to that of Reference Example 8.



40

Reference No.	R¹	R²	R³	R⁴	n	x	Yield (%)	m.p. (°C)	
45	9	Me	H	H	H	O	Cℓ	43	105-106
10	Me	Ph	H	H	O	Cℓ	62	138-140	
11	Et	H	H	H	O	Cℓ	63	93-94	
50	12	Et	Ph	H	H	O	Cℓ	71	123-127
13	Pr	H	H	H	O	Cℓ	78	Syrup	
14	Pr	Ph	H	H	O	Cℓ	94	Syrup	
15	Bu	H	H	H	O	Cℓ	81	Syrup	
55	16	Bu	Ph	H	H	O	Cℓ	82	Syrup
17	Ph	Ph	H	H	O	Cℓ	50	163-165	

Continuation of the Table on the next page

(continued)

	Reference No.	R ¹	R ²	R ³	R ⁴	n	x	Yield (%)	m.p. (°C)
5	18	Me	H	H	H	1	Cℓ	59	Syrup
10	19	Me	Ph	H	H	1	Cℓ	83	Syrup
15	20	Et	H	H	H	1	Cℓ	83	Syrup
20	21	Et	H	H	Me	1	Br	56	Syrup
25	22	Et	H	Me	H	1	Cℓ	77	Syrup
30	23	Et	Ph	H	H	1	Cℓ	100	Syrup
35	24	Pr	H	H	H	1	Cℓ	75	Syrup
40	25	Pr	H	H	Me	1	Br	47	Syrup
45	26	Pr	H	Me	H	1	Cℓ	74	Syrup

	Reference No.	R ¹	R ²	R ³	R ⁴	n	x	Yield (%)	m.p. (°C)
20	27	Pr	Ph	H	H	1	Cℓ	90	Syrup
25	28	Pr	Ph	Me	H	1	Cℓ	75	Syrup
30	29	Bu	H	H	H	1	Cℓ	73	Syrup
35	30	Bu	Ph	H	H	1	Cℓ	93	Syrup
40	31	Bzl	H	H	H	1	Cℓ	96	Syrup
45	32	Ph	H	H	H	1	Cℓ	85	Syrup
50	33	Ph	Ph	H	H	1	Cℓ	80	Syrup
55	34	Me	H	H	H	2	Cℓ	64	Syrup
60	35	Et	H	H	H	2	Br	48	Syrup
65	36	Pr	H	H	H	2	Cℓ	69	Syrup
70	37	Pr	Ph	H	H	2	Cℓ	87	Syrup
75	38	Bu	H	H	H	2	Cℓ	78	Syrup
80	39	Pr	NO ₂	H	H	O	Cℓ	99	Syrup
85	40	Pr	NO ₂	H	H	1	Cℓ	98	Syrup
90	41	Pr	NO ₂	H	H	2	Cℓ	98	Syrup
95	42	Bzl	Ph	H	H	1	Cℓ	67	Syrup

Reference Example 436-Chloro-1-cyanomethyl-3-propylpyrimidine-2,4(1H,3H)-dione

Chloroactonitrile(16.5 g) and potassium carbonate (29.3 g) were added to a solution of 6-chloro-3-propylpyrimidine-2,4(1H,3H)-dione (20 g) in DMF (200 ml), and the mixture was stirred at room temperature for 24 hours. The reaction solution was concentrated and evaporated to dryness to obtain a residue. A resulting residue was dissolved in chloroform and H₂O, and the organic layer was washed with water and dried. The solvent was evaporated to dryness to give a syrup, which was purified by column chromatography on silica gel to give a crystalline product. Recrystallization of the crude crystals from ethyl acetate-isopropylether gave colorless prisims (21.1 g, 87%), mp. 83 - 84°C.

Reference Example 446-Chloro-1-cyanomethyl-5-phenyl-3-propylpyrimidine-2,4(1H,4H)-dione

- 5 The captioned compound was synthesized by methods similar to that of Reference Example 43.
 M.p. 194 - 195°C

10 The sulfur-containing fused pyrimidine derivatives (compounds (I)) represented by general formula (I) and the salts thereof according to the present invention have inhibitory activities on vasoconstriction, bronchus smooth muscle constriction and the activity of reducing the infarct size in ischemic and reperfused heart to mammals including humans, and therefore are useful as therapeutic and ameliorative agents for myocardial infarction, angina pectoris and asthma.

15 Compounds (I) and the salts thereof have also inhibitory activities on IL-1 production, anti-inflammatory activity, antipyretic activity and analgesic activity, and therefore are useful as therapeutic and ameliorative agents for rheumatoid arthritis, lumbago, cervico-omo-brachial syndrome and scabies. Further, the compounds are useful for treatment of cerebral lesions and memory impairment (for example, Alzheimer's disease) through inducing the production of NGF.

15 The toxicity of compounds (I) is low. Hence, compounds (I) of the present invention or a salt thereof, when used as pharmaceutical drugs, can be safely administered parenterally or orally in the forms of powders, granules, tablets, capsules, injections, suppositories and ointments, solely or in combination with pharmaceutically acceptable additional components, such as vehicles, disintegrators, lubricants, binders, dispersants, plasticizers or diluents.

20 The dosage is dependent on the type of disease to be treated, the symptom of the disease, the subject to whom the drugs are administered and the method of administration. For example, when orally administered to adult patients with myocardial infarction or angina pectoris, it is advantageous that the active ingredients (compounds (I)) are normally administered in one dose of about 0.1 to 30 mg/kg of weight, preferably about 0.5 to 10 mg/kg of weight, about once to 3 times a day.

25 Of the sulfur-containing fused pyrimidine derivatives represented by general formula (I) and the salts thereof according to the present invention, pyrimido[6,1-b][1,3]thiazepin-7,9(8H)-diones are novel in their skeleton itself as described above. It is industrially extremely useful to provide these structurally novel compounds.

The present invention will be described in detail with the following Examples, Preparation Examples and Experimental Examples. It is understood of course that these are not intended to limit the scope of the invention.

In this specification, the following abbreviations are used.

- 30 Me: methyl, Et: ethyl, Pr: propyl, Bu: butyl,
 All: allyl, Bzl: benzyl, Ph: phenyl, Ac: acetyl,
 s: singlet, d: Doublet, t: Triplet, q: quartet,
 m: multiplet, brs: broad signal.

Example 19-Phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

40 Sodium hydrosulfide (3.3 g) was added to a solution of 6-chloro-1-(3-chloropropyl)-5-phenyl-3-propyluracil (7 g) in DMF (60 ml) little by little under ice cooling and the mixture was stirred for 1 hour. The reaction solution was concentrated to dryness. The residue was dissolved in methylene chloride-H₂O, and the organic layer was washed with water and dried. The solvent was evaporated and the resulting crude crystals were recrystallized from methanol to give colorless crystals (3.85 g, 62%).

Melting point: 132-133°C

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Elemental analysis for C ₁₆ H ₁₈ N ₂ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	63.55 ;	6.00 ;	9.26
Found:	63.59 ;	6.05 ;	9.23

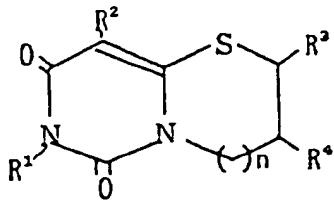
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1H-NMR(CDCl₃)δ: 0.94(3H,t), 1.42-1.93(2H,m),
 2.02-2.37(2H,m), 2.92(2H,t), 3.94(2H,t),
 4.08(2H,t), 7.08-7.50(5H,m)

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Examples 2 to 36

The following compounds were synthesized by methods similar to that of Example 1.



Example No.	R'	R'	R'	n	χ_{f}^{δ} d	$\text{mp} (\text{ }^{\circ}\text{C})$	$^{1}\text{H-NMR} (\delta) (\text{90MHz}) \delta$
2	Me	H	H	0	61	147-148	(CDC d_3) ; 3.26(3H, s), 3.35(2H, t), 4.32(2H, t), 5.68(1H, s).
3	Me	Ph	H	0	55	215-217	(CDC d_3) ; 3.24(2H, t), 3.35(3H, s), 4.41(2H, t), 7.36(5H, s).
4	Et	H	H	0	72	124-125	(CDC d_3) ; 1.19(3H, t), 3.37(2H, t), 4.33(2H, t), 3.93(2H, q), 5.67(1H, s).
5	Pr	H	H	0	69	137-139	(CDC d_3) ; 0.92(3H, t), 1.40-1.85(2H, m), 3.36(2H, t), 3.83(2H, q), 4.31(2H, t), 5.65(1H, s).
6	Pr	Ph	H	0	55	128-129	(CDC d_3) ; 0.93(3H, t), 1.46-1.91(2H, m), 3.20(2H, t), 3.91(2H, t), 4.37(2H, t), 7.38(5H, s).
7	Bu	H	H	0	70	121-123	(CDC d_3) ; 0.92(3H, t), 1.10-1.85(4H, m), 3.35(2H, t), 3.90(2H, t), 4.31(2H, t).
8	Bu	Ph	H	0	61	123-124	(CDC d_3) ; 0.92(3H, t), 1.13-1.85(4H, m), 3.22(2H, t), 3.93(2H, t), 4.40(2H, t), 7.39(5H, s).
9	Allyl	H	H	0	55	126-129	(CDC d_3) ; 3.35(2H, t), 4.31(2H, t), 4.47(2H, d), 5.02-5.37(2H, m), 5.67(1H, s), 5.63(1H, m).
10	Ph	H	H	0	86	226-228	(d ₆ -DMSO) ; 3.45(3H, t), 4.23(3H, t), 5.84(1H, s), 7.10-7.60(5H, m).
11	Ph	H	H	0	78	231-232	(CDC d_3) ; 3.26(2H, t), 4.43(2H, t), 7.16-7.56(10H, m).
12	Me	H	H	1	67	153-154	(CDC d_3) ; 2.08-2.41(2H, m), 3.06(2H, t), 4.00(2H, t), 3.32(3H, s), 5.71(1H, s).
13	Me	Ph	H	1	51	157-159	(CDC d_3) ; 1.99-2.35(2H, m), 2.92(2H, t), 4.09(2H, t), 3.40(3H, s), 7.13-7.55(5H, m).

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Example N°.	R ¹	R ²	R ³	R ⁴	n	$\{g\}^{1d}$	mP (°C)	¹ H-NMR (δ) (90MHz) δ
14	t-Bu	II	II	II	1	71	142-143	(CDC ₆) ; 1.00(3H, t), 2.09-2.41(2H, m), 3.08(2H, t), 3.97(2H, q), 4.01(2H, t), 5.69(1H, s).
15	t-Bu	II	II	Me	1	46	97- 98	(CDC ₆) ; 1.19(3H, t), 1.40(3H, d), 1.60-2.07(1H, m), 2.22-2.55(1H, m), 3.29-3.80(2H, m), 3.95(2H, q), 4.27-4.53(1H, m), 5.63(1H, s).
16	t-Bu	II	Me	II	1	67	73- 75	(CDC ₆) ; 1.19(3H, t), 1.20(3H, d), 2.04-2.52(1H, m), 2.61-3.39(3H, m), 3.86(2H, q), 4.21-4.42(1H, m), 5.69(1H, s).
17	t-Bu	Ph	II	II	1	60	141-143	(CDC ₆) ; 1.27(3H, t), 2.03-2.35 (2H, m), 2.91(2H, t), 4.02(2H, q), 4.08(2H, t), 7.10-7.53(5H, m).
18	t-Pr	II	II	II	1	55	83- 85	(CDC ₆) ; 0.93(3H, t), 1.40-1.90(2H, m), 2.10-2.40(2H, m), 3.09(2H, t), 3.75-4.10(4H, m), 5.71(1H, s).
19	t-Pr	II	Me	II	1	26	93- 94	(CDC ₆) ; 0.92(3H, t), 1.41(3H, d), 1.39-2.06(3H, m), 2.21-2.56(1H, m), 3.28-3.70(2H, m), 4.25-4.56(1H, m), 5.63(1H, s).
20	t-Pr	II	Me	II	1	32	87- 88	(CDC ₆) ; 0.92(3H, t), 1.17(3H, d), 1.42-1.87(2H, m), 2.06-2.52(1H, m), 2.59-3.42(2H, m), 3.86(3H, t), 4.21-4.46(1H, m), 5.67(1H, s).
21	t-Pr	Ph	II	Me	1	61	118-119	
22	Bu	II	II	II	1	58	73- 75	(CDC ₆) ; 0.93(3H, t), 1.10-1.90(4H, m), 2.00-2.40(2H, m), 2.92(2H, t), 3.96(2H, t), 4.10(2H, t).
23	Bu	Ph	II	II	1	43	123-126	(CDC ₆) ; 0.93(3H, t), 1.04-1.84(4H, m), 2.02-2.34(2H, m), 2.91(2H, t), 3.97(2H, t), 4.07(2H, t), 7.12-7.53(5H, m).

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Example N _{o.}	R ¹	R ²	R'	n	χ_{g} Id	m.p. (°C)	¹ H-NMR (δ) (90MHz) &
24	H ₂ T	H	H	1	55	142-143	(CDC ₆ ,); 1.99-2.32(2H, ^m), 2.99(2H,t), 3.93(2H,t), 5.09(2H,s), 5.71(1H,s), 7.10-7.56(5H, ^m).
25	pH	H	H	1	66	186-188	(d ₆ -DMSO); 2.0-2.3(2H, ^m), 3.10(2H,t), 3.86(2H, ^m), 5.71(1H,s), 7.10-7.60(5H, ^m).
26	pH	pH	H	1	59	217-219	(CDC ₆ ,); 2.06-2.38(2H, ^m), 2.95(2H,t), 4.09(2H,t), 7.15-7.47(10H, ^m).
27	pH	H	H	2	33	68- 69	(CDC ₆ ,); 1.70-2.20(4H, ^m), 2.99(2H,t), 3.31(3H,s), 4.38(2H,t), 6.06(1H,s).
28	pH	H	H	2	30	78- 79	(CDC ₆ ,); 1.27(3H,l), 1.69-2.20(4H, ^m), 2.99(2H,t), 4.37(2H,t), 3.96(2H,q), 6.03(1H,s).
29	pT	H	H	2	42	69- 70	(CDC ₆ ,); 0.93(3H,t), 1.40-2.10(6H, ^m), 2.85(2H,t), 2.80-3.05(2H, ^m), 3.86(2H,t), 4.26-4.50(2H, ^m).
30	pT	pH	H	2	54	136-138	(CDC ₆ ,); 0.94(3H,t), 1.48-2.11(6H, ^m), 2.85(2H,t), 3.94(2H,t), 4.45(2H,t), 7.11-7.48(5H, ^m).
31	Hn	H	H	2	52	30- 35	(CDC ₆ ,); 0.93(3H,t), 1.10-2.20(8H, ^m), 2.80-3.30(2H, ^m), 3.90(2H,t), 4.26-4.46(2H, ^m), 6.04(1H,s).
32	pT	N0,	H	0	47	189-191	(CDC ₆ ,); 0.93(3H,t), 1.43-1.90(2H, ^m), 3.40(2H,t), 3.88(2H,t), 4.57(2H,t).
33	pT	N0,	H	1	40	123-124	(CDC ₆ ,); 0.93(3H,t), 1.38-1.90(2H, ^m), 2.15-2.49(2H, ^m), 3.13(2H,t), 3.92(2H,t), 4.14(2H,t).

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Example No.	R ¹	R ²	R ³	n	V _g ¹ d	m.p. (°C)	¹ H-NMR (δ) (90MHz) δ
34	Pr	NO ₂	H	2	23	103-110	(CDCl ₃): 0.94(3H, t), 1.40-2.23(6H, m), 3.08(2H, t), 3.91(2H, t), 4.43(2H, t).
35	Pr	H	C ₁₁ H ₂₀ OII	0	52	103-104	(CDCl ₃): 0.91(3H, t), 1.39-1.84(2H, m), 3.60-4.05(5H, m), 4.20(1H, q), 4.43(1H, q), 5.66(1H, s).
36	BzI	Ph	H	1	60	155-157	(CDCl ₃): 2.12-2.28(2H, m), 2.92(2H, t), 4.07(2H, t), 5.16(2H, s) 7.21-7.60(10H, m)

Example 371-Oxo-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

m-Chloroperbenzoic acid (3.78 g) was added to a solution of 9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (6 g) in methylene chloride (90 ml) little by little with stirring under ice cooling and the mixture was stirred under ice cooling for 6 hours. The insoluble material was removed by filtration, and the filtrate was washed with an aqueous sodium bicarbonate. After drying, it was concentrated to dryness. The residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from methylene chloride-isopropyl ether to give colorless needles (5.7 g, 90%).

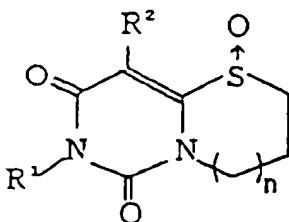
Melting point: 190-192°C

Elemental analysis for C ₁₆ H ₁₈ N ₂ O ₃ S:			
	C(%)	H(%)	N(%)
Calcd:	60.36 ;	5.70 ;	8.80
Found:	59.93 ;	5.67 ;	8.42

1H-NMR(CDCl₃)δ: 0.94(3H,t), 1.47-1.92(2H,m),
 2.00-2.89(3H,m), 3.09-3.44(1H,m),
 3.96(2H,t), 4.09-4.82(2H,m), 7.39(5H,s)

Examples 38 to 57

The following compounds were synthesized by methods similar to that of Example 37.



Example No.	R¹	R²	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
38	Me	Ph	O	64	169-172	(CDCl ₃); 2.75-3.34(2H,m), 3.38(3H,s), 4.63-4.92(2H,m), 7.35-7.60(5H,m).
39	Et	Ph	O	70	164-166	(CDCl ₃); 1.25(3H,t), 2.73-3.14(1H,m), 3.20-3.47(1H,m), 4.05(2H,q), 4.51-5.00(2H,m), 7.35-7.65(5H,m).
40	Bu	Ph	O	82	175-177	(CDCl ₃); 0.95(3H,t), 1.13-1.85(4H,m), 2.75-3.15(1H,m), 3.21-3.48(1H,m), 3.99(2H,t), 4.52-4.89(2H,m), 7.35-7.63(5H,m).
41	Ph	Ph	O	64	292-293	(DMSO-d ₆); 3.08-3.81(2H,m), 4.25-4.94(2H,m), 7.17-7.74(10H,m).
42	Me	Ph	1	68	204-207	(CDCl ₃); 2.07-2.88(3H,m), 3.10-3.40(1H,m), 3.40(3H,s), 4.13-4.77(2H,m), 7.21-7.52(5H,m).
43	Et	Ph	1	56	212-214	(CDCl ₃); 1.26(3H,t), 2.07-2.90(3H,m), 3.10-3.44(1H,m), 4.06(2H,q), 4.10-4.81(2H,m), 7.39(5H,s).
44	Pr	Ph	1	90	190-192	(CDCl ₃); 0.94(3H,t), 1.47-1.92(2H,m), 2.00-2.89(3H,m), 3.09-3.44(1H,m), 3.96(2H,t), 4.09-4.82(2H,m), 7.39(5H,s).
45	Bu	Ph	1	72	142-144	(CDCl ₃); 0.94(3H,t), 1.06-1.85(4H,m), 2.02-2.93(3H,m), 3.13-3.48(1H,m), 4.01(2H,t), 4.13-4.83(2H,m), 7.40(5H,s).
46	Ph	Ph	1	79	241-244	(CDCl ₃); 2.06-2.96(3H,m), 3.13-3.47(1H,m), 4.14-4.73(2H,m), 7.15-7.54(10H,m).
47	Pr	H	O	85	120-122	

Continuation of the Table on the next page

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(continued)

Example No.	R ¹	R ²	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
5	48	Pr	Ph	O	87	205-207 (CDCl ₃);0.95(3H,t),1.46-1.91(2H,m),2.74-3.15(1H, m),3.21-3.48(1H,m),3.94(2H,t),4.64-4.90(2H,m), 7.36-7.63(5H,m).
10	49	Bzl	Ph	1	78	201-203 (CDCl ₃);2.22-2.43(1H,m),2.52-2.65(1H,m), 2.64-2.79(1H,m),3.25-3.38(1H,m),4.25-4.40(1H,m), 4.64-4.76(1H,m),5.20(2H,s),7.26-7.58(10H,m).

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	Exam ple No.	R ¹	R ²	n	Yield (%)	m. p. (°C)	¹ H-NMR (δ)
5	50	Pen	Ph	1	95	158-159	(CDCl ₃); 0.90(3H, t), 1.30-1.40(4H, m), 1.61-1.75(2H, m), 2.22-2.44(1H, m), 2.51-2.82(2H, m), 3.25-3.40(1H, m) 4.00(2H, t), 4.33(1H, ddd), 4.26(1H, ddd), 7.34-7.52(5H, m).
10	51	Hex	Ph	1	68	115-116	(CDCl ₃); 0.88(3H, t), 1.25-1.40(6H, m), 1.58-1.72(2H, m), 2.25-2.46(1H, m), 2.50-2.82(2H, m), 3.26-3.41(1H, m), 4.00(2H, t), 4.27-4.41(1H, m), 4.64-4.77(1H, m), 7.35-7.51(5H, m).
15	52	Hep	Ph	1	72	126-127	(CDCl ₃); 0.87(3H, t), 1.21-1.40(8H, m), 1.59-1.72(2H, m), 2.25-2.45(1H, m), 2.53-2.83(2H, m), 3.26-3.40(1H, m), 4.00(2H, t), 4.34(1H, ddd), 4.70(1H, ddd) 7.34-7.50(5H, m).
20	53	-CH ₂ - 	Ph	1	78	201-203	(DMSO-d ₆); 2.22-2.43(1H, m), 2.52-2.65(1H, m), 2.64-2.79(1H, m), 3.25-3.38(1H, m), 4.25-4.40(1H, m), 4.64-4.76(1H, m), 5.20(2H, s), 7.26-7.58(10H, m).
25	54	-CH ₂ - 	Ph	1	96	158-160	(CDCl ₃); 2.19-2.42(1H, m), 2.51-2.68(1H, m), 2.66-2.80(1H, m), 3.23-3.39(1H, m), 3.79(3H, s), 4.32(1H, ddd), 4.70(1H, ddd), 5.17(2H, dd), 6.81-6.87(1H, m), 7.09-7.50(8H, m).
30	55	-CH ₂ - 	Ph	1	87	160-162	(CDCl ₃); 2.19-2.42(1H, m), 2.50-2.77(2H, m), 3.22-3.37(1H, m) 3.78(3H, s), 4.30(1H, ddd), 4.69(1H, ddd) 5.12(2H, s), 6.83(2H, dt), 7.51(2H, dt), 7.28-7.47(5H, m).
35	56	-CH ₂ - 	Ph	1	83	228-231	(CDCl ₃); 2.22-2.47(1H, m), 2.50-2.63(2H, m), 3.25-3.40(1H, m), 3.34(1H, ddd), 4.70(1H, ddd), 5.15(2H, ddd), 7.24-7.31(1H, m), 7.33-7.62(8H, m).
40	57	-CH ₂ - 	Ph	1	88	199-200	(CDCl ₃); 2.23-2.48(1H, m), 2.51-2.87(2H, m), 3.36(1H, ddd), 4.36(1H, ddd), 4.70(1H, ddd), 5.35(2H, s), 7.10-7.23(3H, m), 7.33-7.49(6H, m).
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Example 581,1-Dioxo-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

5 m-Chloroperbenzoic acid (0.66 g) was added to a solution of 1-oxo-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g) in methylene chloride (20 ml) little by little with stirring under ice cooling. The reaction mixture was stirred at 5°C for 1.5 hours, and further stirred at room temperature for 20 hours. The insoluble material was removed by filtration, and the filtrate was washed with a saturated aqueous sodium bicarbonate. After drying, the organic layer was concentrated to dryness. The resulting crude crystals were recrystallized from methylene chloride-hexane to give colorless needles (0.77 g, 73%).

10 Melting point: 179-180°C

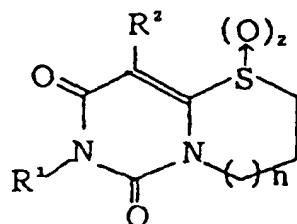
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Elemental analysis for C ₁₆ H ₁₈ N ₂ O ₄ S:			
	C(%)	H(%)	N(%)
Calcd:	57.47 ;	5.43 ;	8.38
Found:	57.07 ;	5.42 ;	8.75

20 ¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.45-1.91(2H,m),
2.26-2.62(2H,m), 3.30(2H,t), 3.93(2H,t),
4.24(2H,t), 7.21-7.51(5H,m)

Examples 59 to 67

25 The following compounds were synthesized by methods similar to that of Example 58.



Example No.	R¹	R²	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
40 59	Me	Ph	O	70	188-189	(CDCl ₃); 3.43(3H,s), 3.43(2H,t), 4.30(2H,t), 7.49(5H,s).
60	Et	Ph	O	68	210-211	(CDCl ₃); 1.26(3H,t), 3.41(2H,t), 4.05(2H,q), 4.28(2H,t), 7.43(5H,s).
45 61	Pr	Ph	O	72	157-158	(CDCl ₃); 0.95(3H,t), 1.45-1.91(2H,m), 3.42(2H,t), 3.94(2H,t), 4.29(2H,t), 7.48(5H,s).
62	Bu	Ph	O	87	160-161	(CDCl ₃); 0.94(3H,t), 1.05-1.81(4H,m), 3.42(2H,t), 3.99(2H,t), 4.29(2H,t), 7.48(5H,s).
50 63	Ph	Ph	O	56	247-249	(CDCl ₃); 3.38(2H,t), 4.24(2H,t), 7.14-7.65(10H,m).
64	Me	Ph	1	33	188-189	(CDCl ₃); 2.26-2.62(2H,m), 3.31(2H,t), 3.41(3H,s), 4.26(2H,t), 7.19-7.52(5H,m).
55 65	Et	Ph	1	71	206-208	(CDCl ₃); 1.25(3H,t), 2.23-2.55(2H,m), 3.29(2H,t), 4.22(2H,t), 4.02(2H,q), 7.22-7.53(5H,m).

Continuation of the Table on the next page

(continued)

Example No.	R ¹	R ²	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
5	66	Bu	Ph	1	77	173-174 (CDCl ₃); 0.93(3H,t), 1.04-1.84(4H,m), 2.24-2.60(2H,m), 3.31(2H,t), 3.97(2H,t), 4.25(2H,t), 7.19-7.51(5H,m).
10	67	Ph	Ph	1	77	277-279 (CDCl ₃); 2.29-2.62(2H,m), 3.35(2H,t), 4.29(2H,t), 7.13-7.56(10H,m).

Example 689-Phenyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

Boron trifluoride (0.68 ml) was added to a solution of 7-benzyl-9-phenyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g) in toluene (40 ml) and was refluxed for 14 hours. Methanol (7 ml) was added to the reaction solution and the mixture was stirred for 30 minutes. The resulting solution was concentrated to dryness, and the residue was dissolved in methylene chloride and ethyl ether. The insoluble material was obtained by filtration and the product was washed by aqueous methanol. After the washing, it was recrystallized from DMF-water to give colorless crystals (0.33 g, 44%).

Melting point: >300°C

Elemental analysis for C ₁₃ H ₁₂ N ₂ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	59.98 ;	4.65 ;	10.76
Found:	59.90 ;	4.65 ;	10.79

¹H-NMR(200MHz, DMSO-d₆) δ: 2.04-2.16(2H,m), 2.99(2H,t), 3.89(2H,t), 7.14-7.21(2H,m), 7.29-7.42(3H,m), 11.37(1H, brs)

Examples 697-Pentyl-9-phenyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

1-Iodopentane (2.29 g), potassium carbonate (1.28 g) and 9-phenyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (2 g) in DMF (30 ml) were stirred at 100°C for 15 hours. The reaction solution was concentrated to dryness, and the residue was purified by column chromatography on silica gel. The obtained crude crystals were recrystallized from ethyl acetate-hexane to give colorless crystals (1.64 g, 65%).

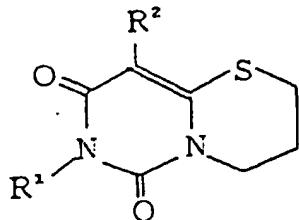
Melting point: 100-101°C

Elemental analysis for C ₁₈ H ₂₂ N ₂ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	65.43 ;	6.71 ;	8.48
Found:	65.69 ;	6.80 ;	8.44

¹H-NMR(200MHz, CDCl₃) δ: 0.89(3H,t), 1.26-1.42(4H,m), 1.60-1.73(2H,m), 2.19-2.31(2H,m), 2.96(2H,t), 3.97(2H,t), 4.11(2H,t), 7.23-7.29(2H,m), 7.35-7.46(3H,m).

Examples 70 to 77

The following compounds were synthesized by methods similar to that of Example 69.



Exam ple No.	R¹	R²	Yield (%)	m. p. (°C)	¹ H-NMR(200MHz,CDCl ₃) δ
15	70 	Ph	85	191-192	2.19-2.31(2H,m), 2.98(2H,t), 4.11(2H,t), 5.31(2H,s), 7.11-7.47(9H,m).
20	71 	Ph	87	188-190	2.15-2.28(2H,m), 2.93(2H,t), 4.08(2H,t), 3.78(3H,s), 5.10(2H,s), 6.83(2H,d), 7.53(2H,d), 7.21-7.28(2H,m), 7.36-7.48(3H,m).
25	72 	Ph	92	Oily product	2.15-2.28(2H,m), 2.92(2H,t), 4.07(2H,t), 3.78(3H,s), 5.14(2H,s), 6.78-6.83(1H,m), 7.07-7.47(8H,m).
30	73 	Ph	100	Oily product	2.16-2.29(2H,m), 2.94(2H,t), 4.08(2H,t), 5.12(2H,s), 7.20-7.53(9H,m),
35	74 	Ph	80	196-197	2.16-2.29(2H,m), 2.95(2H,t), 4.09(2H,t), 5.12(2H,s). 7.22-7.31(4H,m), 7.35-7.54(5H,m).
40	75 	Ph	80	151-152	2.18-2.30(2H,m), 2.96(2H,t), 4.10(2H,t), 5.27(2H,s), 6.99-7.10(2H,m), 7.18-7.48(7H,m).
45	76 Hex	Ph	65	77-78	0.87(3H,t), 1.25-1.44(6H,m), 1.59-1.75(2H,m), 2.18-2.30(2H,m), 2.95(2H,t), 3.97(2H,t), 4.10(2H,t), 7.23-7.30(2H,m), 7.34-7.46(3H,m).
50	77 Hep	Ph	73	Oily product	0.87(3H,t), 1.22-1.41(8H,m), 1.59-1.74(2H,m), 2.18-2.30(2H,m), 2.95(2H,t), 3.97(2H,t), 4.11(2H,t), 7.23-7.29(2H,m), 7.35-7.47(3H,m).

Examples 782-Hydroxy-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

- 5 Trifluoroacetic anhydride (3.78 g) and triethylamine (1.82 g) were added to a solution of 1-oxo-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (4 g) in methylene chloride (60 ml) and the mixture was stirred at 40°C for 60 hours. The reaction solution was evaporated to dryness, and the residue was dissolved in methylene chloride-H₂O. Then, the organic layer was washed with a saturated aqueous sodium bicarbonate. After drying, the organic solution was concentrated, and the resulting residue was purified by column chromatography on silica gel.
- 10 The resulting crude crystals were recrystallized from methylene chloride-isopropyl ether to give colorless needles (3.1 g, 78%).

Melting point: 170-171°C

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Elemental analysis for C ₁₆ H ₁₈ N ₂ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	60.36 ;	5.70 ;	8.80
Found:	60.03 ;	5.68 ;	8.58

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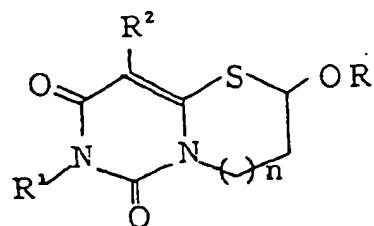
¹H-NMR(CDCl₃)δ: 0.89(3H,t), 1.41-1.87(2H,m),
2.23-2.99(2H,q), 3.88(2H,t),
3.97-4.39(2H,m), 4.52(1H,d), 5.07(1H,q),
7.07-7.43(5H,m).

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Examples 79 to 82

The following compounds were synthesized by methods similar to that of Example 78.

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Example No.	R ¹	R ²	R	n	Yield (%)	m.p. (°C)	¹ H-NMR(δ)
79	Pr	H	H	O	45	168-169	(d ₆ -DMSO); 0.86(3H,t), 1.31-1.77(2H,m), 3.72(2H,t), 4.15-4.33(2H,m), 5.72(1H,s), 5.87(1H,brs), 7.27(1H,d).
80	Pr	H	Ac	O	75	Syrup	(CDCl ₃); 0.93(3H,t), 1.43-1.87(2H,m), 2.11(3H,s), 3.84(2H,t), 4.25(1H,q), 4.71(1H,d), 5.69(1H,s), 6.26(1H,d).
81	Bu	Ph	H	1	85	170-172	(CDCl ₃); 0.92(3H,t), 1.27-1.45(2H,m), 1.56-1.71(2H,m), 2.21-2.31(2H,m), 3.46(1H,brs), 3.96(2H,t), 4.00-4.15(1H,m), 4.21-4.33(1H,m), 5.24(1H,q), 7.18-7.43(5H,m).
82	Bzl	Ph	H	1	53	238-241	(d ₆ -DMSO); 2.03-2.18(1H,m), 2.27-2.42(1H,m), 4.06(2H,t), 5.03(2H,s), 5.45(1H,q), 6.96(1H,d), 7.17-7.44(10H,m).

Example 831-Oxo-9-phenyl-7-propyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

5 m-Chloroperbenzoic acid (0.34 g) was added to a solution of 9-phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (0.53 g) in methylene chloride (10 ml) little by little with stirring under ice cooling, and then, the reaction mixture was stirred at room temperature for 10 hours. An insoluble material was removed by filtration, and the filtrate was washed with a saturated aqueous sodium bicarbonate. After drying, the organic solution was concentrated to dryness. The resulting residue was purified column chromatography on silica gel. The resulting crude crystals were
10 recrystallized from methylene chloride-isopropyl ether to give colorless needles (0.47 g, 87%).

Melting point: 174-175°C

Elemental analysis for C ₁₆ H ₁₆ N ₂ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	60.74 ;	5.10 ;	8.85
Found:	60.76 ;	5.07 ;	8.60

20 ¹H-NMR(CDCl₃)δ: 0.96(3H,t), 1.48-1.94(2H,m),
3.28(1H,se), 3.81(1H,g), 3.99(2H,t)
5.53(1H,se), 7.4(5H,m), 7.68(1H,q)

Example 849-Phenyl-2-phenylthio-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

Boron trifluoride ethyl etherate (0.2 ml) was added to a solution of 2-hydroxy-7-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (0.6 g) and thiophenol (0.23 g) in methylene chloride (10 ml) and the mixture was stirred at room temperature for 70 hours. The reaction solution was evaporated to dryness, and the residue was dissolved in methylene chloride. The solution was washed with 1N aqueous sodium hydroxide and water, followed by drying. The solvent was evaporated and the resulting syrup was crystallized from ethyl acetate-hexane to give colorless crystals (0.68 g, 85%).

Melting point: 126-127°C

Elemental analysis for C ₂₂ H ₂₂ N ₂ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	64.36 ;	5.40 ;	6.82
Found:	64.17 ;	5.39 ;	6.77

45 ¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.87-2.71(2H,m),
3.93(2H,t), 3.79-4.68(3H,m)
7.14-7.52(10H,m)

Example 852-Ethoxy-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

50 A 2-ethoxy derivative (syrup, 92%) was obtained by a method similar to that of Example 69.

55 ¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.46-1.91(2H,m),
3.12-3.78(2H,m), 3.93(2H,t),
3.85-4.47(2H,m), 4.96(1H,t)
7.16-7.45(5H,m).

Example 86

8-Nitro-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione

5 6-Propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7-(6H)-dione (2.12 g) was added to concentrated sulfuric acid
(5.2 ml) little by little under ice cooling, and then, fuming nitric acid (1.8 ml) was added dropwise thereto with stirring.
The mixture was stirred under ice cooling for 1 hour. The reaction temperature was kept under 5°C for this period. The
reaction solution was poured on ice water, and the resulting crystals were collected by filtration and recrystallization
from ethanol-ethyl acetate to give pale yellow needles (2.0 g, 85%).
10 Melting point: 189-191°C

10 Melting point: 189-191°C

Elemental analysis for C ₉ H ₁₁ N ₃ O ₄ S			
	C(%)	H(%)	N(%)
Calcd:	42.02 ;	4.31 ;	16.33
Found:	41.97 ;	4.34 ;	16.22

¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.43-1.90(2H,m),
3.40(2H,t), 3.88(2H,t), 4.57(2H,t)

Example 87

9-Acetylaminomethyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

25 Zinc powder (1.21 g) was added to a solution of 9-nitro-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g) in acetic acid (10 ml) and the mixture was refluxed for 4 hours. An insoluble material was removed by filtration, and the filtrate was concentrated to obtain syrup. The syrup was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from methylene chloride-hexane to give colorless needles (0.83 g, 79%).

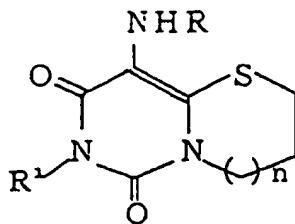
³⁰ Melting point: 172-174°C

Elemental analysis for C ₁₂ H ₁₇ N ₃ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	50.87 ;	6.05 ;	14.83
Found:	50.85 ;	6.04 ;	14.84

¹H-NMR(CDCl₃)δ: 0.92(3H,t), 2.15(3H,s), 3.01(2H,t),
3.88(2H,t), 4.03(2H,t), 7.35(1H,brs)

Examples 88 to 91

The following compounds were synthesized by methods similar to that of Example 87.



	Example No.	R ¹	R	n	Yield (%)	m.p. (°C)	¹ H-NMR(δ)
5	88	Pr	CHO	O	50	156-160	(d ₆ -DMSO); 0.86(3H,t), 1.33-1.79(2H,m), 3.40(2H,t), 3.75(2H,t), 4.32,(2H,t), 8.11(1H,s), 9.30(1H,brs).
10	89	Pr	CHO	1	75	166-167	(CDCl ₃); 0.91(3H,t), 1.42-1.87(2H,m), 2.09-2.43(2H,m), 3.04(2H,t), 3.89(2H,t), 4.04(2H,t), 7.67(1H,brs), 8.28(1H,s).
15	90	Pr	Ac	O	50	203-205	(CDCl ₃); 0.91(3H,t), 1.39-1.85(2H,m), 2.13(3H,s), 3.29(2H,t), 3.85(2H,t), 4.39(2H,t), 7.66(1H,brs).
	91	Pr	CHO	2	77	162-163	(CDCl ₃); 0.93(3H,t), 1.24-2.18(6H,m), 2.94(2H,t), 3.91(2H,t), 4.41(2H,t), 7.82(1H,brs), 8.31(1H,s).

Example 929-Amino-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

20 1N Aqueous hydrochloric acid (10 ml) was added to a solution of 9-formylamino-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (2 g) in methanol (30 ml), and the solution was refluxed for 3 hours. The reaction solution was concentrated to dryness, and the resulting residue was dissolved in water. The solution was neutralized with 1N aqueous sodium hydroxide, and allowed to cool to give colorless needles (1.55 g, 87%).

Melting point: 124-125°C

Elemental analysis for C ₁₀ H ₁₅ N ₃ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	49.77 ;	6.27 ;	17.41
Found:	49.79 ;	6.26 ;	17.44

¹H-NMR(CDCl₃) δ: 0.92(3H,t), 3.37(2H,brs), 3.09(2H,t), 3.91(2H,t), 4.02(2H,t)

Example 938-Amino-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione

40 An 8-amino derivative was obtained by a method similar to that of Example 92 in a 56% yield.
Melting point: 120-122°C

Elemental analysis for C ₉ H ₁₃ N ₃ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	47.56 ;	5.77 ;	18.49
Found:	47.46 ;	5.78 ;	18.48

50 ¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.41-1.88(2H,m), 3.11(2H,brs), 3.35(2H,t), 3.88(2H,t), 4.33(2H,t)

Example 949-Butyrylamino-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

55 Butyric anhydride (1.32 g) and 4-dimethylaminopyridine (20 mg) were added to a solution of 9-amino-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g) in pyridine (20 ml) and the solution was heated at

EP 0 404 525 B1

50°C for 4 hours. The reaction solution was concentrated to dryness, and the residue was dissolved in methylene chloride-water. The organic solution was washed with water, dried and concentrated to dryness. The resulting crude crystals were recrystallized from ethanol-ether to give colorless crystals (0.93 g, 72%).

Melting point: 171-172°C

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Elemental analysis for C ₁₄ H ₂₁ N ₃ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	54.00 ;	6.80 ;	13.49
Found:	53.98 ;	6.81 ;	13.54

15 ¹H-NMR CDCl₃δ: 0.91(3H,t), 1.00(3H,t), 1.41-1.97(4H,m),
2.06-2.46(4H,m), 3.00(2H,t), 3.88(2H,t).
4.04(2H,t), 7.16(1H,brs).

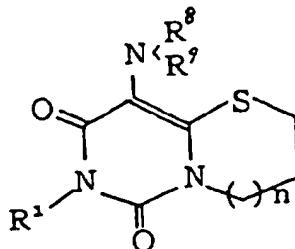
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Examples 95 to 100

The following compounds were synthesized by methods similar to that of Example 94.

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Example No.	R¹	R ⁸	R ⁹	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
95	Pr	Me	Me	O	80	122-150 (Hydrochloride)	(CDCl ₃); 0.91(3H,t), 1.41-1.85(2H,m), 2.68(6H, s), 3.27(2H,t), 3.81(2H,t), 4.35(2H,t).
96	Pr	H	Bu	O	40	143-145 (Hydrochloride)	(CDCl ₃); 0.92(6H,t), 1.13-1.87(6H,m), 2.89(2H, t), 3.31(2H,t), 3.87(2H,t), 4.32(2H,t).
97	Pr	Bu	Bu	O	42	Syrup	(CDCl ₃); 0.88(3H,t), 0.92 (3H,t), 0.94(3H,t), 1.07-1.80 (10H,m), 2.94(4H,t), 3.23 (2H,t), 3.82(2H,t), 4.36(2H, t).
98	Pr	H	COPr	O	73	182-183	(CDCl ₃); 0.93(3H,t), 1.00 (3H,t), 1.38-1.95(4H,m), 2.34(2H,t), 3.27(2H,t), 3.86 (2H,t), 4.39(2H,t), 7.43(1H, brs).

Continuation of the Table on the next page

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(continued)

Example No.	R ¹	R ⁸	R ⁹	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
5 99	Pr	Me	Me	1	45	90-113 (Hydrochloride)	(CDCl ₃) δ : 0.92(3H,t), 1.40-1.88(2H,m), 2.03-2.35 (2H,m), 2.67(6H,s), 2.93 (2H,t), 3.85(2H,t), 3.90(2H, t).
10 100	Pr	H	Bu	1	41	Syrup	(CDCl ₃) δ : 0.92(6H,t), 1.16-1.88(6H,m), 2.05-2.38 (2H,m), 2.83(2H,t), 3.03(2H, t), 3.93(2H,t), 3.99(2H,t).

15 Example 1019-Formyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

20 The Vilsmeier reagent prepared from phosphorus oxychloride (3.7 ml) and DMF (6.2 ml) was added dropwise to a solution of 7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (6 g) in DMF (38 ml) with stirring under ice cooling. The reaction solution was stirred at room temperature for 3 hours and then, poured on ice water. The mixture was stirred for a while and the precipitated crystals were recrystallized from ethyl acetate to give colorless crystals (6.46 g, 95%).

25 Melting point: 153-154°C

25

Elemental analysis for C ₁₀ H ₁₂ N ₂ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	49.99 ;	5.03 ;	11.66
Found:	49.23	5.05 ;	11.56

30 ¹H-NMR(CDCl₃) δ : 0.94(3H,t), 1.45-1.89(2H,m), 3.35(2H,t),
3.89(2H,t), 4.39(2H,t), 10.08(1H,s)

35

Example 1028-Formyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione

40 An 8-formyl derivative was synthesized by a method similar to that of Example 101 in a 62% yield.
Melting point: 153-154°C

40

Elemental analysis for C ₁₀ H ₁₂ N ₂ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	49.99 ;	5.03 ;	11.66
Found:	49.23	5.05 ;	11.56

45

50 ¹H-NMR(CDCl₃) δ : 0.94(3H,t), 1.45-1.89(2H,m), 3.35(2H,t),
3.89(2H,t), 4.39(2H,t), 10.08(1H,s)Example 1032-Cyano-3-(5,7-dioxo-6-propyl-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-8-yl)acrylonitrile

55

A solution of 8-formyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione (1 g), malononitrile (0.31 g) and ethanol (20 ml) containing 10% aqueous solution of potassium hydroxide (0.1 ml), were stirred at 60°C for 7 hours. The reaction solution was concentrated under reduced pressure, and the residue was dissolved in chloroform. After

EP 0 404 525 B1

washing with water and drying, the organic solution was concentrated to dryness. The resulting residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from ethyl acetate-isopropyl ether to give pale yellow-red needles (0.23 g, 19%).

Melting point: 135-137°C

5

Elemental analysis for C ₁₃ H ₁₂ N ₄ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	54.15 ;	4.19 ;	19.43
Found:	53.94 ;	4.02 ;	19.72

10

¹H-NMR(CDCl₃)δ: 0.92(3H,t), 1.49-1.85(2H,m)
3.52(2H,t), 3.86(2H,t), 4.52(2H,t),
7.31(1H,s)

15

Example 104

Ethyl(E)-3-(5,7-dioxo-6-propyl-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-8-yl)acrylate

20

A solvation of the Wittig reagent prepared from triphenylphosphine (5.3 g) and ethyl bromoacetate (3.4 g), (carboethoxymethylene)triphenylphosphorane (6 g) and 8-formyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione (3.76 g) in methylene chloride (15 ml) was refluxed in for 7 hours. The reaction solution was concentrated to dryness. The resulting residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from methylene chloride -isopropyl ether to give colorless needles (3.82 g, 79%).

25

Melting point: 140-141°C

30

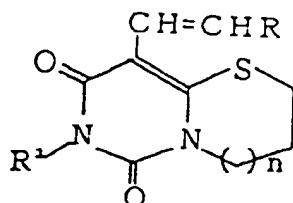
Elemental analysis for C ₁₄ H ₁₈ N ₂ O ₄ S			
	C(%)	H(%)	N(%)
Calcd:	54.18 ;	5.85 ;	9.03
Found:	54.15 ;	5.81 ;	8.95

Examples 105 to 112

35

The following compounds were synthesized by methods similar to that of Example 104.

40



45

Example No.	R ¹	R	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
105	Pr	(Z)-CN	O	54	165-167	(CDCl ₃); 0.93(3H,t), 1.42-1.89(2H,m), 3.40(2H,t), 3.87(2H,t), 4.10(2H,t), 5.49(1H,d), 6.96(1H,d).
106	Pr	(E)-Bu	O	65	63-68	(CDCl ₃); 0.90(3H,t), 0.93(3H,t), 1.10-1.97(6H,m), 2.19(2H,q), 3.31(2H,t), 3.88(2H,t), 4.35(2H,t), 6.08(1H,d), 6.35(1H,dt).

50

Continuation of the Table on the next page

(continued)

Example No.	R ¹	R	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
5	107	Pr	(E)-Ph	O	15	168-170 (CDCl ₃); 0.95(3H,t), 1.42-1.92(2H,m), 3.32(2H,t), 3.89(2H,t), 4.36(2H,t), 6.76(1H,d), 7.13-7.56(6H,m).
10	108	Pr	(Z)-CN	1	43	143-144 (CDCl ₃); 0.93(3H,t), 1.43-1.87(2H,m), 2.09-2.41(2H,m), 3.12(2H,t), 3.91(2H,t), 4.08(2H,t), 5.56(1H,d), 6.84(1H,d).
15	109	Pr	(E)-CN	1	28	154-155 (CDCl ₃); 0.93(3H,t), 1.41-1.87(2H,m), 2.10-2.43(2H,m), 3.16(2H,t), 3.88(2H,t), 4.11(2H,t), 6.79(1H,d), 7.34(1H,d).
20	110	Pr	(E)-COOEt	1	89	128-129 (CDCl ₃); 0.92(3H,t), 1.26(3H,t), 1.40-1.85(2H,m), 2.06-2.39(2H,m), 3.12(2H,t), 3.89(2H,t), 4.10(2H,q), 4.18(2H,t), 7.10(1H,d), 7.72(1H,d).
25	111	Pr	(E)-Bu	1	18	58-60 (CDCl ₃); 0.88(3H,t), 0.91(3H,t), 1.06-1.99(6H,m), 2.01-2.35(4H,m), 3.03(2H,t), 3.89(2H,t), 4.05(2H,t), 6.11(1H,d), 6.55(1H,dt).
	112	Pr	(E)-Ph	1	49	159-160 (CDCl ₃); 0.98(3H,t), 1.60-1.79(2H,m), 2.20-2.34(2H,M), 3.14(2H,t), 3.97(2H,t), 4.14(2H,t), 7.00(1H,d), 7.19-7.51(5H,m), 7.74(1H,d).

Example 1139-Dimethylammoniomethyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione chloride

A mixture of 7-propyl-3,4-dihydro-2H,5H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g), paraformaldehyde (0.22 g) and dimethylamine hydrochloride (0.51 g) in acetic acid (25 ml) was refluxed for 18 hours. The reaction solution was concentrated dryness, and the resulting residue was dissolved in water. Then, the solution was made basic with 1N aqueous sodium hydroxide, followed by extraction of the product with methylene chloride. After washing with water and drying, the organic layer was concentrated to dryness to obtain a syrup. The syrup was converted to the hydrochloride to form crystals, which were recrystallized from ethanol-ethyl acetate to give colorless prisms (0.46 g, 33%).

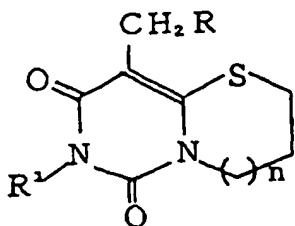
Melting point: 201-203°C

Elemental analysis for C ₁₃ H ₂₁ N ₃ O ₂ S-HCl			
	C(%)	H(%)	N(%)
Calcd:	48.82 ;	6.93 ;	13.14
Found:	48.77 ;	7.19 ;	13.09

¹H-NMR(CDCl₃)δ: 0.92(3H,t), 1.40-1.87(2H,m), 2.03-2.38(2H,m), 2.25(6H,s), 3.03(2H,t), 3.33(2H,s), 3.89(2H,t), 4.04(2H,t)

Examples 114 to 116

The following compounds were synthesized by methods similar to that of Example 113.



Example No.	R ¹	R	n	Yield (%)	m. p. (°C)	¹ H-NMR (δ)
114	Pr	-N< Me Me	0	62	102-104	(CDCl ₃); 0.92(3H, t), 1.42-1.87(2H, m), 2.21(6H, s), 3.21(2H, s), 3.21(2H, t), 3.86(2H, t), 4.30(2H, t).
115	Pr	-N 	0	34	241-246	(CDCl ₃); 0.91(3H, t), 1.23-1.84(8H, m), 2.36(4H, t), 3.14(2H, t), 3.24(2H, s), 3.83(2H, t), 4.25(2H, t).
116	Pr	-N 	1	48	203-210	.

50 Example 117

9-Hydroxymethyl-7-propyl-3,4-dihydro-2H,5H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

55 Sodium borohydride (0.15 g) was added to a solution of 9-formyl-7-propyl-3,4-dihydro-2H,5H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g) in methanol (20 ml), followed by stirring at room temperature for 1 hour. The reaction solution was concentrated to dryness, and the residue was dissolved in water. Then, the solution was made acidic with 1N aqueous hydrochloric acid and extracted with methylene chloride. After washing with water and drying, the organic layer was concentrated to dryness. The resulting residue was purified by column chromatography on silica gel. The

resulting crude crystals were recrystallized from ethyl acetate-isopropyl ether colorless needles (0.43 g, 43%).

Melting point: 134-137°C

Elemental analysis for C ₁₁ H ₁₆ N ₂ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	51.54 ;	6.29 ;	10.93
Found:	51.52 ;	6.32 ;	10.83

- 10 ¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.42-1.88(2H,m),
2.06-2.40(2H,m), 3.09(2H,t), 3.14(1H,t),
3.99(2H,t), 4.06(2H,t), 4.56(2H,d)

15 Example 118

8-Hydroxymethyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione

The compound was synthesized by a method similar to that of Example 117.

Melting point: 141-143 C

Elemental analysis for C ₁₀ H ₁₄ N ₂ O ₃ S:			
	C(%)	H(%)	N(%)
Calcd:	49.57 ;	5.82 ;	11.56
Found:	49.86 ;	5.68 ;	11.78

- 30 ¹H-(CDCl₃)δ: 0.94(3H,t), 1.43-1.88(2H,m), 2.89(1H,t),
3.34(2H,t), 3.86(2H,t), 4.36(H,t)
4.40(2H,d).

Example 119

8-[{(E)-3-Oxo-3-(1-piperidino)propene-1-yl]-6-propyl-2,-3-dihydro-5H-thiazolo[3,2-c]pyrimidine -5,7(6H)-dione

- 35 A solution of 2M trimethylaluminum in hexane (5.3 ml) was added to a solution of piperidine (0.69 g) in methylene chloride (25 ml), followed by stirring at room temperature for 15 minutes. Then, a solution of ethyl(E)-3-(5,7-dioxo-6-propyl-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-8-yl) acrylate (1 g) in methylene chloride (25 ml) was added thereto, followed by heating under reflux for 16 hours. Hydrochloric acid was added to the reaction solution to 25 decompose the unreacted reagents, and then the organic layer was washed with water and dried. The solution was concentrated to dryness, and the resulting residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from methylene chloride-isopropyl ether to give colorless needles (1.03 g, 91%).

Melting point: 237-238°C

Elemental analysis for C ₁₇ H ₂₃ N ₃ O ₃ S			
	C(%)	H(%)	N(%)
Calcd:	58.43 ;	6.63 ;	12.02
Found:	58.07 ;	6.55 ;	11.83

- 50 ¹H-NMR (CDCl₃)δ 0.4 (3H), 4.5-1.9(8H,),
3.39(2H,t), 3.60(4H,brs), 3.89(2H,t)
4.42(2H,t), 7.19(1H,d), 7.67(1H,d)

55

Example 1209-[*(E*)-3-Oxo-3-(1-piperidino) propene-1-yl]-7-propyl-3,4-dihydro-2*H*,6*H*-pyrimido[6,1-*b*][1,3]thiazine-6,8(7*H*)-dione

- 5 The piperidino derivative was synthesized by a method similar to that of Example 119 in 31% yield.
 Melting point: 181-182 °C

Elemental analysis for C ₁₈ H ₂₅ N ₃ O ₃ :			
	C(%)	H(%)	N(%)
Calculated:	59.48 ;	6.93 ;	11.56
Found:	59.20 ;	6.92 ;	11.39

- 15 ¹H-NMR(CDCl₃)δ: 0.97(3H,t), 1.52-1.78(8H,m),
 2.20-2.32(2H,m), 3.14(2H,t),
 25 3.54-3.70(4H,m), 3.94(2H,t), 4.14(2H,t),
 7.76(2H,s).

Example 1212-Chloromethyl-6-propyl-2,3-dihydro-5*H*-thiazolo[3,2-c]pyrimidine-5,7(6*H*)-dione

- 25 Thionyl chloride (0.61 ml) was added dropwise to a solution of 2-hydroxymethyl-6-propyl-2,3-dihydro-5*H*-thiazolo [3,2-c]pyrimidine-5,7(6*H*)-dione (1 g) in methylene chloride (15 ml) with stirring at room temperature, and the solution was refluxed for 16 hours. The solution was concentrated to dryness, and the resulting residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from methylene chloride-isopropyl ether to give colorless crystals (0.9 g, 84%).

Melting point: 85-88°C

Elemental analysis for C ₁₀ H ₁₃ ClN ₂ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	46.06 ;	5.03 ;	10.74
Found:	46.08 ;	5.03 ;	10.74

- 30 ¹H-NMR(CDCl₃)δ: 0.92(3H,t), 1.41-1.87(2H,m),
 3.63-4.22(1H,m), 3.73(2H,s), 3.82(2H,t),
 4.33(1H,q), 5.68(1H,s)

Example 1222-Chloromethyl-8-phenyl-6-propyl-2,3-dihydro-5*H*-thiazolo[3,2-c]pyrimidine-5,7(6*H*)-dione

- 40 45 The compound was obtained by a method similar to that of Example 121.
 Melting point: 112-113°C

Elemental analysis for C ₁₆ H ₁₇ ClN ₂ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	57.05 ;	5.09 ;	8.32
Found:	57.07 ;	5.13 ;	8.47

- 50 55 ¹H-NMR(CDCl₃)δ: 0.95(3H,t), 1.49-1.93(2H,m),
 3.55-4.10(1H,m), 3.66(2H,s), 4.45(1H,q),
 7.38(5H,s).

Example 1232-Phenylthiomethyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione

5 A mixture of 2-chloromethyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione (0.8 g), thiophenol (0.47 ml) and potassium carbonate (0.63 g) was refluxed in ethanol (20 ml) for 42 hours. The solution was concentrated to dryness, and the resulting residue thus obtained was dissolved in methylene chloride and water. After washing with water and drying, the organic solution was concentrated to dryness. The resulting syrup was purified by column chromatography on silica gel to give colorless syrup. This syrup was allowed to stand in a refrigerator to obtain colorless crystals (1.2 g, 95%).

10 Melting point: 88-89°C

Elemental analysis for C ₁₆ H ₁₈ N ₂ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	57.46 ;	5.42 ;	8.38
Found:	57.56 ;	5.45 ;	8.40

20 ¹H-NMR(CDCl₃)δ: 0.92(3H,t), 1.41-1.86(2H,m), 3.17(2H,d),
3.83(2H,t), 4.28, 4.31(each 1H,d),
5.63(1H,s), 7.27-7.53(5H,m)

Example 1242-Methylene-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c] pyrimidine-5,7(6H)-dione

25 Piperidine (0.66 g) and potassium iodide (0.1 g) were added to a solution of 2-chloromethyl-6-propyl-2,3-dihydro-5H-thiazolo[3,2-c]pyrimidine-5,7(6H)-dione (1 g) in ethanol (20 ml). The reaction mixture was stirred at 60°C for 42 hours. The reaction solution was concentrated to dryness, and the residue was dissolved in chloroform. After washing with water and drying, the organic layer was concentrated to dryness. The resulting residue was purified by column chromatography on silica gel. The resulting crystals were recrystallized from methylene chloride-isopropyl ether-hexane to give colorless crystals (0.55 g, 64%).

30 Melting point: 102-103°C

Elemental analysis for C ₁₀ H ₁₂ C ₁ N ₂ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	53.55 ;	5.39 ;	12.49
Found:	53.66 ;	5.37 ;	12.46

40 ¹H-NMR(CDCl₃)δ: 0.93(3H,t), 1.41-1.88(2H,m), 3.84(2H,t),
4.89(2H,t), 5.29(1H,q), 5.42(1H,q),
5.65(1H,s)

Example 125Ethyl (3-amino-6,8-dioxo-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-2-yl)carboxylate

45 A solution of 6-chloro-1-cyanomethyl-3-propylpyrimidine-2,4(1H,3H)-dione (1.5 g), ethyl thioglycolate (0.88 g) and potassium carbonate (1 g) in ethanol (30 ml) was refluxed for 15 hours. The reaction solution was concentrated to dryness, and the resulting residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from ethyl acetate-hexane to give colorless plates (0.23 g, 11%).

50 Melting point: 200-201°C

5

Elemental analysis for C ₁₃ H ₁₇ N ₃ O ₄ S			
	C(%)	H(%)	N(%)
Calcd:	50.15 ;	5.50 ;	13.50
Found:	50.32 ;	5.52 ;	13.40

10 ¹H-NMR(200MHz, CDCl₃)δ: 0.94(3H,t), 1.33(3H,t), 1.56-1.73(2H,m), 3.87(2H,t), 4.24(2H,q), 4.64(2H,s), 5.97(1H,s).

Example 126Ethyl (3-amino-6,8-dioxo-9-phenyl-7-propyl-7,8-dihydro-4H,6H-pyrimido[6,1-b][1,3]thiazine-2-yl)carboxylate

15 The compound was synthesized by a method similar to that of Example 125 in a 39% yield.
Melting point: 172-173°C

20

Elemental analysis for C ₁₉ H ₂₁ N ₃ O ₄ S			
	C(%)	H(%)	N(%)
Calcd:	58.90 ;	5.46 ;	10.85
Found:	58.67 ;	5.52 ;	10.53

25 ¹H-NMR(200MHz, CDCl₃)δ: 0.96(3H,t), 1.21(3H,t), 1.60-1.79(2H,m), 3.94(2H,t), 4.15(2H,q), 4.77(2H,s), 7.30-7.48(5H,m).

Example 1279-Phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

30 A catalytic amount of p-toluenesulfonic acid was added to a solution of 2-hydroxy-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (0.5 g) in toluene (20 ml) and was refluxed for 5 hours. The reaction solution was concentrated to dryness, and the resulting residue was dissolved in methylene chloride. After washing with water and drying, the solution was concentrated to dryness. The resulting crude crystals were recrystallized from ethyl acetate-isopropyl ether to give colorless prisms (0.33 g, 70%).

35 Melting point: 142-144°C

40

Elemental analysis for C ₁₆ H ₁₆ N ₂ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	63.98 ;	5.37 ;	9.33
Found:	63.82 ;	5.52 ;	9.15

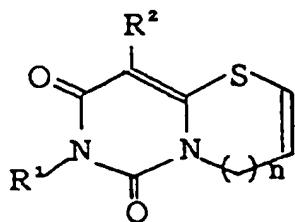
45 ¹H-NMR(CDCl₃)δ: 0.96(3H,t), 1.61-1.80(2H,m), 3.95(2H,t), 4.61(2H,d), 6.31-6.43(2H,m), 7.26-7.48(5H,m)

Examples 128 and 129

50

The following compounds were synthesized by methods similar to that of Example 127.

55



10

Example No.	R¹	R²	n	Yield (%)	m. p. (°C)	¹ H-NMR(δ)
128	Bu	Ph	1	80	131-132	(CDCl ₃); 0.94(3H,t), 1.31-1.48(2H,m), 1.55-1.73(2H,m), 4.00(2H,t), 4.61(2H,d), 6.31-6.44(2H,m), 7.27-7.48(5H,m).
129	Bzl	Ph	1	78	161-164	(CDCl ₃); 4.59(2H,d), 5.18(2H,s), 6.28-6.42(2H,m), 7.26-7.58(10H,m).

20 Example 130

7-Benzyl-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

25 Trifluoroacetic acid anhydride (5.17 g) was added to a solution of 7-benzyl-1-oxo-9-phenyl-3,4-dihydro-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (3 g) in toluene (90 ml) and the mixture was refluxed for 15 hours. The reaction solution was concentrated to dryness, and the resulting residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from methylene chloride-isopropyl ether to give colorless crystals (2.22 g, 78%).

Melting point: 161-164°C

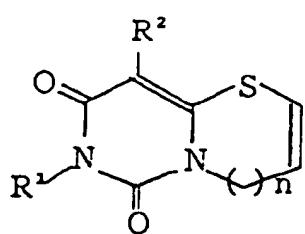
30

Elemental analysis for C ₂₀ H ₁₆ N ₂ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	68.94 ;	4.63 ;	8.04
Found:	69.16 ;	4.67 ;	7.99

35 ¹H-NMR(200MHz, CDCl₃) : 4.59(2H,d), 5.18(2H,s), 6.28-6.42(2H,m), 7.26-7.58(10H,m)

40 Examples 131 to 137

The following compounds were synthesized by methods similar to that of Example 130.



Exam ple No.	R ¹	R ²	n	Yield (%)	m. p. (°C)	¹ H-NMR (200MHz, CDCl ₃) δ
131	Pen	Ph	1	73	95-96	0.89(3H,t), 1.30-1.41(4H,m), 1.61-1.75(2H,m), 3.98(2H,t), 4.61(2H,d), 6.30-6.43(2H,m), 7.25-7.30(2H,m), 7.36-7.48(3H,m).
132	Hex	Ph	1	87	81-82	0.87(3H,t), 1.21-1.45(6H,m), 1.58-1.74(2H,m), 3.98(2H,t), 4.60(2H,d), 6.29-6.43(2H,m), 7.25-7.31(2H,m), 7.37-7.48(3H,m).
133	Hep	Ph	1	95	Syrup	0.87(3H,t), 1.22-1.44(8H,m), 1.58-1.75(2H,m), 3.98(2H,t), 4.61(2H,d), 6.30-6.44(2H,m), 7.26-7.32(2H,m), 7.37-7.49(3H,m).
134		Ph	1	96	Syrup	3.78(3H,s), 4.59(2H,d), 5.15(2H,s), 6.28-6.41(2H,m), 6.78-6.84(1H,m), 7.07-7.30(5H,m), 7.37-7.48(3H,m).
135		Ph	1	94	162-163	3.78(3H,s), 4.58(2H,d), 5.11(2H,s), 6.27-6.40(2H,m), 6.83(2H,dd), 7.27(2H,dd), 7.37-7.55(5H,m).
136		Ph	1	77	231-232	4.62(2H,d), 5.32(2H,s), 6.30-6.44(2H,m), 7.10-7.23(3H,m), 7.28-7.48(6H,m).
137		Ph	1	75	142-143	4.60(2H,d), 5.13(2H,s), 6.29-6.42(2H,m), 7.21-7.30(4H,m), 7.32-7.52(5H,m).

Example 1389-Phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

Boron trifluoride (0.7 ml) was added to a solution of 7-benzyl-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (1 g), in toluene (25 ml) and the mixture was refluxed for 15 hours. Methanol (7.5 ml) was added to the reaction solution at room temperature and the solution was stirred for 30 minutes. The reaction solution was concentrated to dryness, and acetone was added to the resulting residue to obtain the precipitate by filtration. The resulting crude

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crystals were washed and recrystallized from DMF-water to give yellow needles (0.13 g, 18%).

Melting point: 286-290°C

Elemental analysis for C ₁₃ H ₁₀ N ₂ O ₂ S:			
	C(%)	H(%)	N(%)
Calcd:	60.45 ;	3.90 ;	10.85
Found:	60.51 ;	4.02 ;	10.82

- 10 ¹H-NMR(200MHz, CDCl₃)δ: 4.43(2H,dd), 6.41(1H,dt),
6.62(1H,dt), 7.18-7.25(2H,m),
7.34-7.46(3H,m).

15 Example 139

Ethyl 4-(6,8-dioxo-9-phenyl-7,8-dihydro-4H,6H-pyrimido[6,1-b][1,3]thiazine-7-yl)butylate

20 A mixture of 9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (0.9 g), ethyl 4-bromobutylate (1.02 g) and potassium carbonate (0.58 g) in DMF (15 ml) was stirred at 90°C for 15 hours. The reaction solution was concentrated to dryness, and the residue was purified by column chromatography on silica gel. The resulting crude crystals were recrystallized from ethyl ether to give colorless crystals (0.9 g, 69%).

Melting point: 85-86°C

Elemental analysis for C ₁₉ H ₂₀ N ₂ O ₄ S:			
	C(%)	H(%)	N(%)
Calcd:	61.27 ;	5.41 ;	7.52
Found:	61.49 ;	5.43 ;	7.52

- 30 ¹H-NMR(200MHz, CDCl₃)δ: 1.24(3H,t), 1.95-2.10(2H,m),
2.39(2H,t), 4.07(2H,t), 4.12(2H,q), 4.61(2H,d),
6.32-6.44(2H,m), 7.24-7.31(2H,m), 7.37-7.49(3H,m).

35 Example 140

7-(p-Methylbenzyl)-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

40 A mixture of 9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (0.26 g), p-methylbenzylchloride (0.21 g) and potassium carbonate (0.28 g) in DMF (5 ml) was stirred at 100°C for 15 hours. The reaction solution was concentrated to dryness. The resulting residue was dissolved in dichloroethane and was washed with water and dried. m-Chloroperbenzoic acid (0.2 g) was added to the dichloroethane solution little by little under ice cooling, and it was allowed to stand at room temperature for 15 hours. The reaction solution was washed with saturated aq. sodium bicarbonate, and dried, and then trifluoro acetic acid anhydride (0.5 ml) was added thereto and the mixture was refluxed for 15 hours. Oily product obtained by concentration of the resulting solution was dissolved in toluene (20 ml), and a catalytic amount of p-toluenesulfonic acid was added thereto and the mixture was refluxed for 10 hours. The reaction solution was washed with sodium bicarbonate and water, followed by concentration to dryness. The obtained crude crystals were recrystallized from ethyl ether to give colorless crystals (0.12 g, 33%).

Melting point: 124-125°C

Elemental analysis for C ₂₁ H ₁₈ N ₂ O ₄ S:			
	C(%)	H(%)	N(%)
Calcd:	68.91 ;	5.07 ;	7.65
Found:	68.75 ;	4.87 ;	7.51

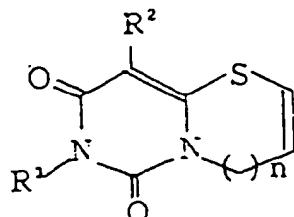
- 50 ¹H-NMR(200MHz, CDCl₃)δ: 2.31(3H,s), 4.57(2H,d),
5.13(2H,s), 6.25-6.42(2H,m), 7.05-7.50(9H,m).

Examples 141 to 155

The following compounds were synthesized by methods similar to that of Example 140.

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Example	R¹	R²	n	Yield (%)	m. p. (°C)	¹ H-NMR (200MHz, CDCl ₃) δ
141	CH ₂ CN	Ph	1	34	159-160	4.63(2H,q), 4.89(2H,s), 6.35-6.45(2H,m), 7.20-7.50(5H,m),
142	-CH ₂ COOEt	Ph	1	60	174-175	1.29(3H,t), 4.23(2H,q), 4.61(2H,d), 4.74(2H,s), 6.35-6.45(2H,m), 7.20-7.50(5H,m).
143	-CH ₂ OPh	Ph	1	45	178-179	4.59(2H,d), 5.14(2H,s), 6.30-6.45(2H,m), 6.70(1H,m), 7.20-7.60(8H,m).
144	F -CH ₂ Ph	Ph	1	82	182-183	4.61(2H,m), 5.28(2H,s), 6.30-6.45(2H,m), 7.05(2H,m), 7.25-7.50(7H,m).
145	Me -CH ₂ Ph	Ph	1	21	165-167	2.47(3H,s), 4.61(2H,d), 5.20(2H,s), 6.25-6.45(2H,m), 7.10-7.50(9H,m).
146	-CH ₂ MnO ₂	Ph	1	57	200-201	4.60(2H,d), 5.24(2H,s), 6.30-6.45(2H,m), 7.27(2H,m), 7.41(3H,m), 7.68(2H,d), 8.16(2H,d).
147	-CH ₂ OAc	Ph	1	57	173-174	4.59(2H,m), 5.13(2H,s), 6.25-6.40(2H,m), 7.26(2H,m), 7.35-7.55(7H,m).

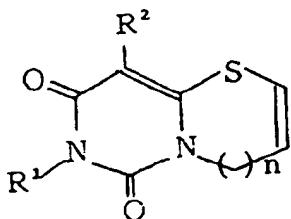
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	Exam ple	R ¹	R ²	n	Yield (%)	m. p. (°C)	¹ H-NMR(200MHz,CDCl ₃) δ
5	148		Ph	1	56	203-204	4.60(2H,d), 5.58(2H,s) 6.30-6.45(2H,m), 7.20-7.60(8H,m), 8.02(1H,d).
10	149		Ph	1	42	154-155	3.86(3H,s), 3.87(3H,s), 4.59(2H,d), 5.12(2H,s), 6.25-6.45(2H,m), 6.80(1H,m), 7.10-7.50(8H,m).
15	150		Ph	1	91	180-188	4.62(2H,d), 5.23(2H,s), 6.25-6.45(2H,m), 7.20-7.80(13H,m),
20	151		Ph	1	61	145-147	2.90-3.05(2H,m), 4.10-4.30(2H,m), 4.62(2H,d), 6.30-6.45(2H,m), 7.20-7.50(10H,m).
25	152		Ph	1	23	166-168	4.62(2H,s), 5.33(2H,s), 6.30-6.45(2H,m), 7.15(1H,m), 7.20-7.50(6H,m), 7.62(1H,m), 8.55(1H,m).
30	153		Ph	1	11	173-175	4.61(2H,d), 5.16(2H,s), 6.30-6.45(2H,m), 7.20-7.55(7H,m), 8.55(2H,m).
35	154		Ph	1	50	201-202	4.59(2H,d), 5.68(2H,s), 6.25-6.40(2H,m), 7.20-7.60(9H,m), 7.83(2H,m), 8.32(1H,d).
40	155		Ph	1	41	140-142	4.64(2H,d), 5.51(2H,s), 6.30-6.45(2H,m), 7.20-7.80(9H,m), 8.07(2H,t).
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The following compounds were synthesized by methods similar to that of Example 130.

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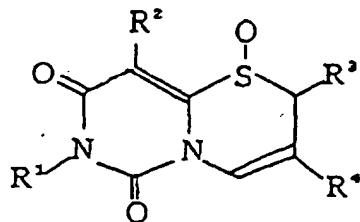
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Example No.	R ¹	R ²	n	Yield (%)	m.p. (°C)	¹ H-NMR(200MHz,CDCl ₃)δ
156	Pr	Ph	O	73	144-145	0.99(3H,t),1.66-1.84(2H,m),4.05(2H,t),6.46(1H,d),7.64(1H,d),7.31-7.56(5H,m).
157	Pr	Ph	2	31	156-157	0.96(3H,t),1.61-1.80(2H,m),2.64-2.73(2H,m),3.94(2H,t),4.74(2H,t),5.82(1H,dt),5.97(1H,dt)7.18-7.26(2H,m),7.35-7.44(3H,m).
158	Pr	H	1	54	Syrup	0.94(3H,t),1.57-1.74(2H,m),3.89(2H,t),4.50(2H,d),5.83(1H,s),6.34(1H,dt),6.41(1H,dt).
159	Pr	COCF ₃	1	10	137-138	0.96(3H,t),1.58-1.77(2H,m),3.89(2H,t),4.50(2H,d),5.83(1H,s),6.34(1H,dt),6.41(1H,d).

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The following compounds were synthesized by the methods similar to that of Example 83.

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Example No.	R ¹	R ²	R ³	R ⁴	Yield (%)	m. p. (°C)	¹ H-NMR(200MHz, CDCl ₃) δ
160	Pr	Ph	H	CH ₃	70	168-171	0.97(3H,t), 1.62-1.80(2H,m), 2.06(3H,d), 3.37(1H,dq), 3.62(1H,d), 3.99(2H,t), 7.43-7.50(6H,m).
161	Bu	Ph	H	H	85	179-180	0.96(3H,t), 1.31-1.49(2H,m), 1.56-1.75(2H,m), 3.35(1H,dt), 3.84(1H,dd), 4.04(2H,dt), 5.57(1H,dt), 7.48(5H,s), 7.71(1H,dd).
162	-CH ₂ - 	Ph	H	H	83	185-186	3.31(1H,dt), 3.81(1H,dd), 5.21(2H,s), 5.51-5.60(1H,m), 7.20-7.57(10H,m), 7.69(1H,dd).
163	-CH ₂ - 	Ph	H	H	88	192-193	3.31(1H,dt), 3.79(3H,s), 3.82(1H,dd), 5.18(2H,s), 5.51-5.61(1H,m), 6.82-6.87(1H,m), 7.08-7.53(8H,m), 7.68(1H,dd).
164	-CH ₂ - 	Ph	H	H	83	203-204	3.34(1H,dt), 3.83(1H,dd), 5.16(2H,s), 5.53-5.63(1H,m), 7.21-7.31(2H,m), 7.37-7.53(7H,m), 7.69(1H,dd).

Example 1652-Hydroxy-1-oxo-3-methyl-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

The compound was synthesized by a method similar to that of Example 78 in a 58% yield.

Melting point: 185-186°C

NMR(200MHz, CDCl₃)δ : 0.95(3H,t), 1.17(3H,d),
1.59-1.79(2H,m), 2.20-2.44(1H,m), 2.75(1H, brs),
3.58-3.79(1H,m), 3.94(2H,t), 4.36(1H,dd),
4.91-5.05(1H,m), 7.20-7.29(2H,m), 7.35-7.46(3H,m).

Example 1667-Benzyl-9-phenyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

Phosphorus trichloride (0.2 ml) was added dropwise to a solution of 7-benzyl-1-oxo-9-phenyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (0.4 g) in DMF (8 ml) under stirring at -10°C. The mixture was stirred at the same temperature for 30 minutes and the resulting solution was poured to ice-water to give crystals and the crystals were collected by filtration. The resulting crude crystals were washed and recrystallized from methylene chloride-methanol

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to give colorless needles (0.31 g, 81%).

Melting point: 202-203°C

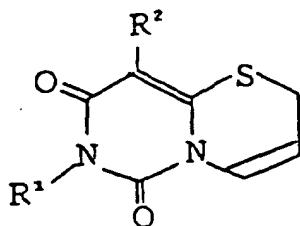
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Elemental analysis for C ₂₀ H ₁₆ N ₂ O ₂ S			
	C(%)	H(%)	N(%)
Calcd:	68.94 ;	4.63 ;	8.04
Found:	68.33 ;	4.78 ;	7.92

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The following compounds were synthesized by a method similar to that of Example 166.

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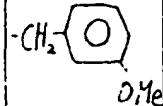
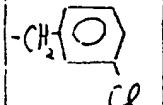
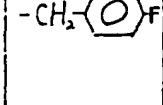
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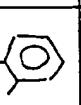
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Example No.	R ¹	R ²	Yield (%)	m.p. (°C)	¹ H-NMR (200MHz, CDCl ₃) δ
167	Pr	Ph	48	167-168	0.96(3H,t), 1.30-1.48(2H,m), 1.60-1.74(2H,m), 3.26(2H,dd), 4.01(2H,t), 5.63(1H,dt), 7.25-7.32(2H,m), 7.37-7.49(4H,m).
168	Bu	Ph	50	88-89	0.95(3H,t), 1.30-1.48(2H,m), 1.60-1.74(2H,m), 3.26(2H,dd), 4.01(2H,t), 5.63(1H,dt), 7.25-7.32(2H,m), 7.37-7.49(4H,m).
169		Ph	78	111-112	3.25(2H,dd), 3.79(3H,s), 5.17(2H,s), 5.62(1H,dt), 6.79-6.86(1H,m), 7.08-7.31(6H,m), 7.37-7.48(3H,m).
170		Ph	83	166-167	3.27(2H,dd), 5.15(2H,s), 5.64(1H,dt), 7.23-7.31(4H,m), 7.38-7.54(6H,m).
171		Ph			

Example No.	R ¹	R ²	Yield (%)	m. p. (°C)	¹ H-NMR(200MHz, CDCl ₃) δ
172	-CH ₂ - 	Ph			
173	-CH ₂ - 	Ph			
174	-CH ₂ - 	Ph			
175	-CH ₂ - 	Ph			
176	-CH ₂ - 	Ph			
177	-CH ₂ - 	Ph			
178	-CH ₂ - 	Ph			
179	-CH ₂ - 	Ph			

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Example 1803-Methyl-9-phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione

50

The compound was synthesized by a method similar to that of Example 127 in a 70% yield.
 Melting point: 146-147°C

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NMR(200MHz, CDCl₃)δ: 0.96(3H,t), 1.61-1.80(2H,m),
 2.04(3H,s), 3.96(2H,t), 4.51(2H,s), 5.98(1H,s),
 7.25-7.30(2H,m), 7.36-7.48(3H,m).

Preparation Examples

When the compounds of the present invention are used as therapeutic preparations for diseases such as myocardial infarction, angina pectoris, renal failure, chronic rheumatism asthma, cerebral lesion and impairment of memory, they can be prepared in accordance with, for example, the following formulations:

1. Tablet

10	(1) 9-Phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (2) Lactose (3) Cornstarch (4) Microcrystalline cellulose (5) Magnesium stearate	10 mg 35 mg 150 mg 30 mg 5 mg <hr/> 230 mg
15		

(1), (2), (3), two thirds of (4) and one half of (5) are mixed and then granulated. The remainders of (4) and (5) are added to the granules, and the mixture is pressed to form a tablet.

2. Capsule

25	(1) 9-Phenyl-7-butyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (2) Lactose (3) Microcrystalline cellulose (4) Magnesium stearate	10 mg 100 mg 70 mg 10 mg <hr/> 190 mg
30		

(1), (2), (3) and one half of (4) are mixed, and then granulated. The remainder of (4) is added to the granules, and the whole is encapsulated in a gelatin capsule.

3. Ointment

35	(1) 1,1-Dioxo-9-phenyl-7-propyl-3,4-dihydro-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione (2) Macrogol 400 (3) Macrogol 4000	2.5 g 70.0 g 27.5 g <hr/> 100.0 g
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(2) and (3) are heated, and (1) is dissolved therein, followed by gradual cooling with stirring to form an ointment.

Experiment 1Inhibitor effects of the compounds on endothelium induced contraction in porcine coronary arteries

(Process)

50 Ring preparation of porcine left anterior descending coronary arteries (LAD) were suspended in 20 ml baths containing Krebs-Henseleit solutions at 37°C gassed with 97% O₂-3% CO₂. Endothelin (3 X 10⁻⁹ M) was added to the baths, and after the constriction reached the steady state, the compounds at concentrations of 10⁻⁶ and 10⁻⁵ M (Examples 45, 48 and 127) were added to the bath. Then, the relaxation activity was examined. The relaxation activity of the compounds was expressed as % inhibition from the maximum contraction by endothelin.

(Results)

The results are shown in Table 1. As shown in Table 1, the following compounds inhibited the endothelin constriction at concentrations of 10^{-6} M and 10^{-5} M in a concentration dependent manner.

5

Table 1

Example No.	Inhibition (%)	
	10^{-6}	10^{-5} (M)
45	6.2	100
48	24.6	86.6
127	82.3	90.0

15 Experiment 2

Inhibitor effects on endothelin induced pressor and depressor responses in conscious beagle dogs.

(Process)

20 Using 10 male beagles (12-14 kg, 8-10 months old), a polyethylene cannula (PEG-100) was inserted into each of the left femoral artery and vein of each beagle after pentobarbital anesthesia. The experiment was started from 3 to 7 days after the operation. The cannula was connected to a pressure transducer to measure the systemic blood pressure. The endothelin antagonistic activity of the compound obtained in Example 65 was examined, taking the depressor and pressor responses due to the intravenous administration of endothelin as its indication. The compound was orally or intravenously administered 5 minutes before the administration of endothelin.

(Results)

30 When 100 pmol/kg of endothelin was intravenously administered, the systemic blood pressure transiently reduced (about 30 mm Hg), and then gradually increased (about 20 mm Hg). As shown below, the intravenous administration of the compound at a dose of 1 mg/kg (Table 2) and the oral administration of the compound in a dose of 10 mg/kg (Table 3) significantly inhibited the depressor and pressor responses due to endothelin. Its inhibitory activity was continuously sustained, for 6 hours by the intravenous administration (i. v.) and for more than 8 hours in the oral administration (p. o.).

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Table 2

Compound (127) (1 mg/kg, i.v.)					
Elapsed Time after Administration	5 min	1 hr	2 hr	4 hr	6 hr
Pressor Response	100	55±7	55±7	38±15	32±10
Depressor Response	86±9	74±11	57±10	31±13	30±8

45 The numerical values indicate % inhibition ± standard error (%) (n = 4).

Table 3

Compound (127) (10 mg/kg, p.o.)				
Elapsed Time after Administration	1 hr	2 hr	4 hr	8 hr
Pressor Response	37±10	85±10	76±12	43±4
Depressor Response	34±9	81±10	67±12	50±0

55 The numerical values indicate % inhibition ± standard error (%) (n = 3).

Experiment 3Depressing Effect against Evolution of infarct size in ischemic and reperfused rat heart

5 Male Wistar rats were medianly dissected under pentobarbital anesthesia, and left anterior descending coronary artery was occluded at its origin for 1 hour, followed by resumption of blood flowing. The chest was closed 30 to 60 minutes after the reperfusion, and the rats were kept under conscious state. After 24 hours, the rats were anesthetized again and the hearts were excised. The left ventricle of each heart was divided into six parts, and these divided parts were stained with 1% triphenyltetrazolium chloride solution at 37°C for 15 minutes. Then, infarcted portions were
10 weighed.

The compound obtained in Example 127 was orally administered in a dose of 100 mg/kg as a gum arabic suspension 2 hours before the occlusion and 5 hours after the reperfusion.

(Results)

15 The results are shown in Table 4. As shown in Table 4, with respect to a control group ($N = 12$), the myocardial infarct size was 36.7 ± 1.4 % of the weight of left ventricles. In contrast, in treated group, myocardial infarct size was significantly reduced, showing the size of 26.8 ± 3.1 %.

Table 4

Control Group	Compound (127)-Administered Group
36.7 ± 1.4 (12)	26.8 ± 3.1 **(5)

The numerical values indicate the ratio of the weight of the infarcted region to the weight of the left ventricles \pm standard error (%). The numerical values in parentheses indicate the number of experiments.
** $P < 0.01$ (vs. control)

Experiment 4Inhibitory Effects on Interleukin 1 Production stimulated by Lipopolysaccharide in the Rat Intraperitoneal Macrophage

(Process)

30 Male Sprague-Dawley rats (8 weeks old, body weight: 300 g, Clea Japan) were killed by exsanguination under etherization. 20 ml of a culture solution (RPMI-1640) was intraperitoneally administered to each rat, and the abdominal part thereof was massaged, followed by abdominal section to recover the culture solution. After centrifugation of the solution, the cell pellet obtained was resuspended in 4 ml of the culture solution, superposed on 5 ml of Ficoll-Paque solution (lymphocyte separation medium, Wako Junyaku, Japan), and centrifuged at 450 g at room temperature for 15 minutes. The cells located in the boundary between the Ficoll-Paque solution and the culture solution were collected
35 and washed 3 times with the culture solution. The resulting cells were suspended in the culture solution again, which was used as a macrophage-suspended solution (3×10^5 cells/ml).

40 Interleukin 1 was produced in the following manner. Macrophage (3×10^5 cells) in a 96-well microtiterplate was preincubated in a CO_2 incubator for 1 hour with each of the compounds shown in Table 5. Then, 50 ug/ml of lipopolysaccharide (*Escherichia coli* 0111 B4, Difco) was added thereto. After cultivation was further continued for 20 hours,
45 the activity of interleukin 1 in the culture supernatant was measured by an LAF (lymphocyte activating factor) assay. Experiments were carried out in a triplicate manner.

50 The LAF assay was conducted as the following. Thymocytes ($1-1.5 \times 10^6$ cells) of C3H/HeJ mice were added to phytohemagglutinin (PHA) P (diluted 1/2000; Difco) and the macrophage culture solution diluted 1/10 or 1/30, and cultivated in a CO_2 incubator. After 48 hours, 3H -thymidine of 0.5 uCi was added thereto and cultivation was further continued for 24 hours. Then, the amount of 3H -thymidine entrapped in the thymocytes was measured. The radioactivity entrapped in the thymocytes was taken as the amount of interleukin 1.

We conducted this process partly modifying the method of R.C. Newton et al. [J. Leukocyte Biology 39, 299-3111 (1986)].

55 (Results)

The results are shown in Table 5. As shown in Table 5, it was found that the following compounds had the inhibitory effects on the production of interleukin 1 in the lipopolysaccharide-stimulated rat intraperitoneal macrophage.

Table 5

Example No.	Inhibition (%)	
	10 ⁻⁵	10 ⁻⁶ (Molar Concentration)
17	93	NT
43	52	NT
45	75	30
50	98	58
59	89	NT
62	96	NT
63	98	NT
64	100	60
65	100	40
67	98	10

Experiment 5Activity of Depressing Fever of Rat Due to Lipopolysaccharide (LPS)

25 (Process)

Male Jcl;SD rats 7 weeks old (body weight: about 250 g, Clea Japan) were used. Each group had 6 rats. The rats were reared in individual cages from the day before, and then the basal body temperature was measured in the rectums using a digital thermometer (Model D221-6, Takara Kogyo) 3 times at intervals of 1 hour. After the third measurement of the body temperature, the compounds shown in Table 6 were orally administered in a volume of 1 ml per 100 g of body weight. LPS (*Escherichia coli* 0111 B4, Difco) was administered at their tail veins in an amount of 0.2 ml per 100 g of body weight 1 hour after the administration of the compounds.

The body temperature was measured from 3 to 5 hours after that at intervals of 1 hour. The antipyretic activity of the compounds was evaluated by the difference in body temperature between a control group and a compound-administered group. Statistical analysis was carried out by the Dunnett's test.

(Results)

40 The results are shown in Table 6. As shown in Table 6, it was found that the following compounds had antipyretic activities in LPS-induced febrile rats.

Table 6

Example No.	Dose (mg/kg,p.o.)	Antipyretic Activity (°C)
64	25	-0.68**
	50	-0.82*
	100	-1.13**
23	100	-0.72**
43	100	-0.70**
65	100	-0.95**
101	100	-0.87**
106	100	-0.53*

* P < 0.05 (vs. control)

** P < 0.01 (vs. control)

Experiment 6Promoting effects of the compounds on synthesis and secretion of NGF in glia cells

5 (Process)

A 48 well-plate was seeded with glia strains cells (C6 glioma) at a rate of 2.5×10^4 cells/well, which was cultivated in Dulbecco's modified eagle's medium (DMEM) containing 10% fetal calf serum. When the cells became confluent (2 to 3 days), each of the following compounds of the present invention was added thereto, and it was cultivated in serum free-DMEM for 24 hours. NGF secreted in the culture supernatant was assayed by enzyme immuno assay. An amount of NGF is shown in a relative value to 100, the value of control (without addition of the compound). The compounds were added in a solution of DMSO, at an amount of 1/100 (V/V) of a medium (V/V). In a control, DMSO alone was added.

10 (Results)

15

As shown in Table 7, the following compounds showed a promoting activity of synthesis and secretion of NGF in a concentration of 10^{-6} and 10^{-5} M.

Table 7

Example No.	Promoting Activity (%)	
	3×10^{-5}	3×10^{-6} (M)
1	117 ± 34	168 ± 6
36	102 ± 2	240 ± 16
58	140 ± 2	164 ± 25
61	109 ± 12	177 ± 8
129	117 ± 6	197 ± 9

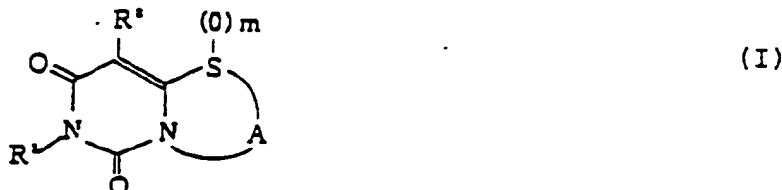
30 The numerical values indicate average of three times experiments \pm standard error.

Claims

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Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound represented by the formula (I) or a pharmacologically acceptable salt thereof:



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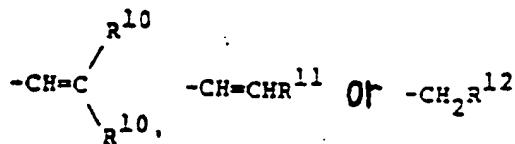
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wherein R^1 represents (1) an alkyl group of 1 to 8 carbon atoms or alkenyl group of 2 to 8 carbon atoms which may be substituted by cyano, carbamoyl, pyridyl, quinolyl, hydroxyl, C_1 to C_4 alkoxy, amino, C_1 to C_4 alkyl, carboxyl, C_1 to C_4 alkoxy-carbonyl or C_2 to C_6 alkanoylamino groups, (2) an aralkyl group, which is obtained by combining a phenyl or naphthyl group with an alkylene group of 1 to 4 carbon atoms, in which the phenyl or naphthyl group may be substituted by 1 to 3 halogen atoms, C_1 to C_4 alkyl, phenyl, o-cyano-phenyl, methoxy, ethoxy or nitro or (3) a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C_1 to C_4 alkyl, methoxy, ethoxy or nitro groups; R^2 represents (1) hydrogen, (2) an aliphatic hydrocarbon group of formula:

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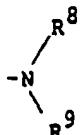
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wherein R¹⁰ represents a cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl, R¹¹ represents a C₁ to C₈ alkyl, phenyl, naphthyl, cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl group, and R¹² represents dimethylamino, diethylamino, morpholino, piperidino or piperazino, (3) a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, methoxy, ethoxy or nitro group, (4) an unsubstituted or substituted amino group of formula:

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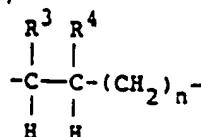
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wherein each of R⁸ and R⁹ is hydrogen, an alkyl group of 1 to 8 carbon atoms or a fatty acid-derived acyl group of 1 to 8 carbon atoms, (5) a formyl group, (6) a nitro group or (7) a halogeno group; A represents a saturated or unsaturated divalent hydrocarbon chain of 2 to 4 carbon atoms selected from (1) a group of the formula:

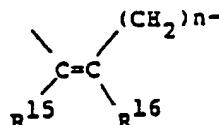
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wherein R³ represents (1) hydrogen, (2) C₁ to C₄ alkyl which may be substituted by an halogen atom, or an C₁ to C₄ alkylthio or phenylthio group, (3) -YR⁵ wherein Y is -O- or -S- and R⁵ is hydrogen, C₁ to C₄ alkyl or a phenyl or naphthyl group which may be substituted by C₁ to C₄ alkyl, C₁ to C₄ alkoxy or phenyl, which may be substituted by 1 to 3 halogen atoms, or a fatty acid-derived acyl group of 1 to 4 carbon atoms; R⁴ represents hydrogen or an alkyl group of 1 to 4 carbon atoms; and n represents an integer of 0 to 2, (2) a group of the formula:

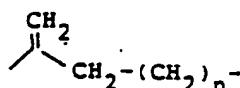
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wherein R¹⁵ and R¹⁶ represents hydrogen, C₁ to C₄ alkyl, -COOR¹⁷ wherein R¹⁷ is hydrogen, C₁ to C₄ alkyl or -NHR¹⁸ wherein R¹⁸ is hydrogen, C₁ to C₄ alkyl or C₁ to C₄ alkanoyl; and n represents an integer of 0 to 2 or (3) a formula:

40

45



wherein n represents an integer of 0 to 2; and m represents an integer of 0 to 2.

2. A compound according to Claim 1, wherein R¹ represents an alkyl group of 1 to 8 carbon atoms, or an alkenyl group of 2 to 8 carbon atoms.

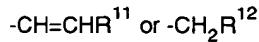
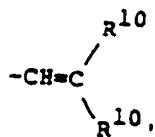
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3. A compound according to Claim 1, wherein R¹ represents an aralkyl group, which is obtained by combining a phenyl or naphthyl group with an alkylene group of 1 to 4 carbon atoms.

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4. A compound according to Claim 1, wherein R¹ represents a phenyl or naphthyl group.

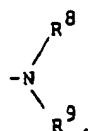
5. A compound according to Claim 1, wherein R² represents a group of the formula:



wherein R¹⁰ represents a cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl, R¹¹ represents a C₁ to C₈ alkyl, phenyl, naphthyl, cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl group, and R¹² represents dimethylamino, diethylamino, morpholino, piperidino or piperazine.

- 15
6. A compound according to Claim 1, wherein R² represents a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, methoxy, ethoxy or nitro groups.

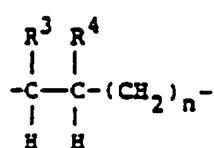
7. A compound according to Claim 1, wherein R² represents a group of the formula:



wherein each of R⁸ and R⁹ is hydrogen, an alkyl group of 1 to 8 carbon atoms or a fatty acid-derived acyl group of 1 to 8 carbon atoms.

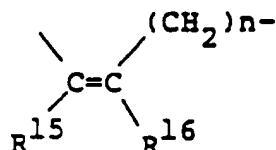
- 25
8. A compound according to Claim 1, wherein R² represents a halogeno group which is selected from fluorine, chlorine, bromine and iodine.

- 30
9. A compound according to Claim 1, wherein A is represented by the formula:



wherein R³ represents (1) hydrogen, (2) C₁ to C₄ alkyl which may be substituted by halogen, C₁ to C₄ alkylthio or phenylthio (3) -YR⁵ wherein Y is -O- or -S-, and R⁵ is hydrogen, C₁ to C₄ alkyl or phenyl or naphthyl which may be substituted by C₁ to C₄ alkyl, C₁ to C₄ alkoxy or phenyl which may be substituted by 1 to 3 halogen atoms, or a fatty acid-derived acyl group of 1 to 4 carbon atoms; R⁴ represents hydrogen or an alkyl group of 1 to 4 carbon atoms; and n represents an integer of 0 to 2.

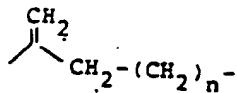
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10. A compound according to Claim 1, wherein A is represented by the formula:



50

wherein R¹⁵ and R¹⁶ represent (1) hydrogen, (2) C₁ to C₄ alkyl, (3) -COOR¹⁷ (wherein R¹⁷ is hydrogen or C₁ to C₄ alkyl), or (4) NHR¹⁸ (wherein R¹⁸ is hydrogen, C₁ to C₄ alkyl or C₁ to C₄ alkanoyl); and n represents an integer of 0 to 2.

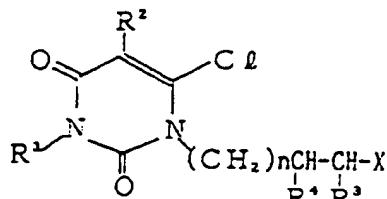
- 55
11. A compound according to Claim 1, wherein A is represented by the formula:



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wherein n represents an integer of 0 to 2.

12. A compound according to Claim 1, wherein R^1 represents (1) an alkyl group of 3 to 8 carbon atoms which may be substituted by cyano, carbamoyl, pyridyl, quinolyl, hydroxyl, C_1 to C_4 alkoxy, amino, C_1 to C_4 alkyl, carboxyl, C_1 to C_4 alkoxycarbonyl or C_2 to C_6 alkanoylamino or (2) an aralkyl group, which is obtained by combining a phenyl or naphthyl group with an alkylene group of 1 to 4 carbon atoms, in which the phenyl or naphthyl group may be substituted by 1 to 3 halogen atoms, C_1 to C_4 alkyl, phenyl, o-cyano-phenyl, methoxy, ethoxy or nitro groups, R^2 represents a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C_1 to C_4 alkyl, methoxy, ethoxy or nitro groups and A is a divalent hydrocarbon chain of 2 to 3 carbon atoms.
- 15 13. The pharmacologically acceptable salt of a compound represented by formula (I) according to Claim 1, wherein the salt is an inorganic salt selected from the hydrochloride, hydrobromide, sulfate, nitrate and phosphate; or an organic salt selected from the acetate, tartrate, citrate, fumarate and maleate.
- 20 14. A compound according to Claim 1, wherein the carbon chain number of the group A is four.
- 15 15. The compound according to claim 1, which is 9-phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 25 16. The compound according to claim 1, which is 7-benzyl-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
17. The compound according to Claim 1, which is 7-(p -chlorobenzyl)-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 30 18. The compound according to Claim 1, which is 7-benzyl-9-phenyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
19. The compound according to Claim 1, which is 9-phenyl-7-propyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 35 20. A method of producing a compound according to Claim 1, which comprises reacting a compound of the formula (II):

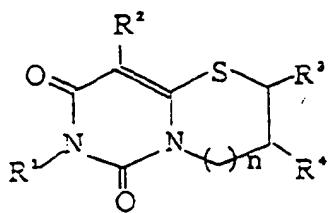


wherein R^1 and R^2 are as defined in Claim 1, with a sulfur reagent selected from N_aSH , $N_{az}S$ and $(NH_4)_2S$ in an organic solvent to obtain a compound of the formula (III):

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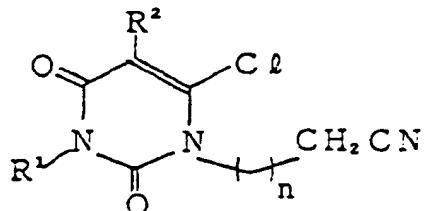
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wherein R³ represents hydrogen, a C₁ to C₄ alkyl group which may be substituted by an halogen atom or a C₁ to C₄ alpylthio or a phenylthio group, -YR⁵ [wherein Y is -O- or --S-, and R⁵ is hydrogen, a C₁ to C₄ alkyl group or a phenyl or naphthyl group which may be substituted by one to three halogen atoms or a fatty acid-derived C₁ to C₄ acyl group; R⁴ represents hydrogen or a C₁ to C₄ alkyl group and n represents an integer of 0 to 2.

15

21. A method of producing a compound (I) according to Claim 1, which comprises reacting a compound of the formula (XXVIII):

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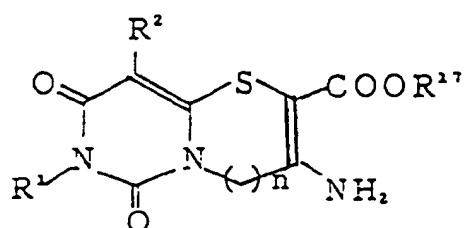
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XXVIII

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with 2 thioglycolic acid in the presence of a base in an organic solvent to obtain a compound of the formula (XXIX):

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XXIX

wherein R¹⁷ is hydrogen or C₁ to C₄ alkyl.

45

22. A method of production according to Claim 20 or 21, further comprising oxidation, nitration, reduction, hydrolysis, alkylation, formylation, halogenation, dehydroxylation, acetalation, thioacetalation, condensation, the Wittig reaction, the Mannich reaction, amidation, nucleophilic substitution, dehydrochlorination, elimination or dealkylation.

50

23. An endothelin inhibiting composition which contains an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable additional components.

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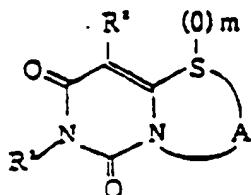
24. An IL-1 inhibiting composition which contains an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable additional components.

25. An NGF stimulating composition which contains an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable additional components.

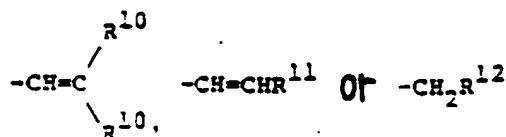
26. A composition according to any of Claims 23 to 25, wherein the pharmaceutically acceptable additional components include vehicles, disintegrators, lubricants, binders, dispersants, plasticizers and diluents.
- 5 27. The use of a compound according to Claim 1 or of a pharmacologically acceptable salt thereof for the manufacture of a medicament for preventing the physiological role of endothelial action.
- 10 28. The use of a compound according to Claim 1 or of a pharmacologically acceptable salt thereof for the manufacture of a medicament for preventing the production of IL-1.
- 15 29. The use of a compound according to Claim 1 or of a pharmacologically acceptable salt thereof for the manufacture of a medicament for stimulating the production of NGF.

Claims for the following Contracting State : ES

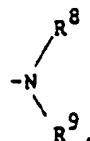
- 15 1. A method of producing a compound represented by the formula (I), or a pharmacologically acceptable salt thereof:



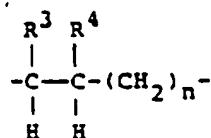
20 25 wherein R¹ represents (1) an alkyl group of 1 to 8 carbon atoms or alkenyl group of 2 to 8 carbon atoms which may be substituted by cyano, carbamoyl, pyridyl, quinolyl, hydroxyl, C₁ to C₄ alkoxy, amino, C₁ to C₄ alkyl, carboxyl, C₁ to C₄ alkoxy-carbonyl or C₂ to C₆ alkanoylamino groups, (2) an aralkyl group, which is obtained by combining a phenyl or naphthyl group with an alkylene group of 1 to 4 carbon atoms, in which the phenyl or naphthyl group may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, phenyl, o-cyano-phenyl, methoxy, ethoxy or nitro or (3) a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, methoxy, ethoxy or nitro groups; R² represents (1) hydrogen, (2) an aliphatic hydrocarbon group of formula:



35 40 wherein R¹⁰ represents a cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl, R¹¹ represents a C₁ to C₈ alkyl, phenyl, naphthyl, cyano, carbamoyl or C₁ to C₄ alkoxy carbonyl group, and R¹² represents dimethylamino, diethylamino, morpholino, piperidino or piperazino, (3) a phenyl or naphthyl group which may be substituted by 1 to 3 halogen atoms, C₁ to C₄ alkyl, methoxy, ethoxy or nitro group, (4) an unsubstituted or substituted amino group of formula:



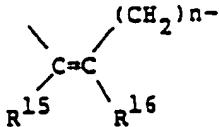
45 50 wherein each of R⁸ and R⁹ is hydrogen, an alkyl group of 1 to 8 carbon atoms or a fatty acid-derived acyl group of 1 to 8 carbon atoms, (5) a formyl group, (6) a nitro group or (7) a halogeno group; A represents a saturated or unsaturated divalent hydrocarbon chain of 2 to 4 carbon atoms selected from (1) a group of the formula:



55 wherein R³ represents (1) hydrogen, (2) C₁ to C₄ alkyl which may be substituted by an halogen atom, or an C₁ to

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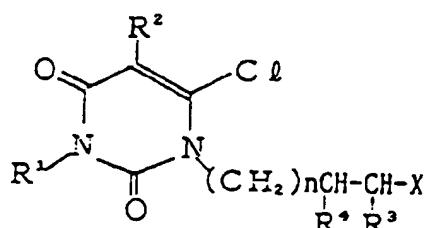
C_4 alkylthio or phenylthio group, (3) - YR^5 wherein Y is -O- or -S- and R^5 is hydrogen, C_1 to C_4 alkyl or a phenyl or naphthyl group which may be substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or phenyl, which may be substituted by 1 to 3 halogen atoms, or a fatty acid-derived acyl group of 1 to 4 carbon atoms; R^4 represents hydrogen or an alkyl group of 1 to 4 carbon atoms; and n represents an integer of 0 to 2, (2) a group of the formula:



10 wherein R^{15} and R^{16} represents hydrogen, C_1 to C_4 alkyl, -COOR¹⁷ wherein R^{17} is hydrogen, C_1 to C_4 alkyl or -NHR¹⁸ wherein R^{18} is hydrogen, C_1 to C_4 alkyl or C_1 to C_4 alkanoyl; and n represents an integer of 0 to 2 or (3) a formula:

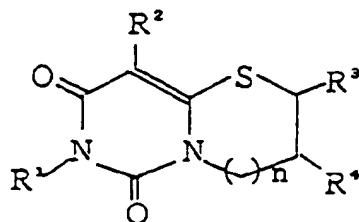


20 wherein n represents an integer of 0 to 2; and m represents an integer of 0 to 2 which method comprises reacting a compound of the formula (II) :



30 II

with a sulfur reagent selected from N_aSH , $N_{az}S$ and $(NH_4)_2S$ in an organic solvent to obtain a compound of the formula (III) :

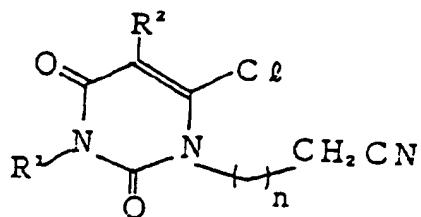


40 III

45 wherein R^3 represents hydrogen, a C_1 to C_4 alkyl group which may be substituted by an halogen atom or a C_1 to C_4 alkythio or a phenylthio group, - YR^5 [wherein Y is -O- or -S-, and R^5 is hydrogen, a C_1 to C_4 alkyl group or a phenyl or naphthyl group which may be substituted by one to three halogen atoms or a fatty acid-derived C_1 to C_4 acyl group; R^4 represents hydrogen or a C_1 to C_4 alkyl group and n represents an integer of 0 to 2.

50 2. A method of producing a compound (I) according to Claim 1, which comprises reacting a compound of the formula (XXVIII) :

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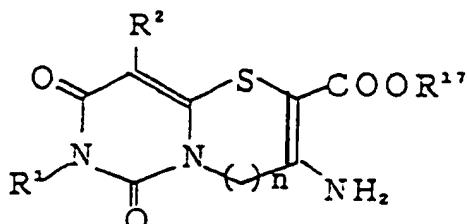
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XXVIII

with a thiglycolic acid in the presence of a base in an organic solvent to obtain a compound of the formula (XXIX):

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wherein R¹⁷ is hydrogen or C₁ to C₄ alkyl.

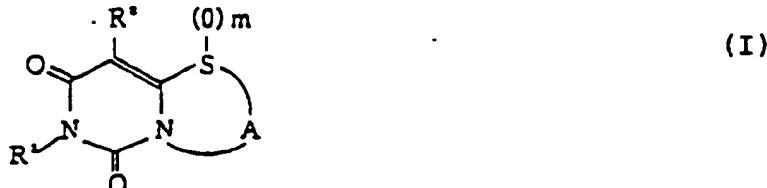
- 3. A method of production according to Claim 1 or 2, further comprising oxidation, nitration, reduction, hydrolysis, alkylation, formylation, halogenation, dehydroxylation, acetalation, thioacetalation, condensation, the Wittig reaction, the Mannich reaction, amidation, nucleophilic substitution, dehydrochlorination, elimination or dealkylation.
- 4. An endotheline inhibiting composition which contains an effective amount of a compound (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable additional components.
- 5. An IL-1 inhibiting composition which contains an effective amount of a compound (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable additional components.
- 6. An NGF stimulating composition which contains an effective amount of a compound (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable additional components.
- 7. A composition according to any of Claims 4-6, wherein the pharmaceutically acceptable additional components are selected from vehicles, disintegrators, lubricants, binders, dispersants, plasticizers and diluents.
- 8. The use of a compound (I) as defined in Claim 1, or of a pharmacologically acceptable salt thereof, for the manufacture of a medicament for preventing the physiological role of endothelial action.
- 9. The use of a compound (I) as defined in Claim 1, or of a pharmacologically acceptable salt thereof, for the manufacture of a medicament for preventing the production of IL-1.
- 10. The use of a compound (I) as defined in Claim 1, or of a pharmacologically acceptable salt thereof, for the manufacture of a medicament for stimulating the production of NGF.
- 11. The use of a compound (I) according to Claim 1, or of a pharmaceutically acceptable salt thereof, for the production of a medicament according to any of Claims 8-10 wherein the said compound (I) is 9-phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.

12. The use of a compound (I) according to Claim 1, or of a pharmaceutically acceptable salt thereof, for the production of a medicament according to any of Claims 8-10, wherein the said compound (I) is 7-benzyl-9-phenyl-4H,6H-pyrimido[6,1-b] [1,3]thiazine-6,8(7H)-dione.
- 5 13. The use of a compound (I) according to Claim 1, or of a pharmaceutically acceptable salt thereof, for the production of a medicament according to any of Claims 8-10, wherein the said compound (I) is 7-(p-chlorobenzyl)-9-phenyl-4H,6H-pyrimido[6,1-b] [1,3]thiazine-6,8(7H)-dione.
- 10 14. The use of a compound (I) according to claim 1, or of a pharmaceutically acceptable salt thereof, for the production of a medicament according to any of Claims 8-10, wherein the said compound (I) is 7-benzyl-9-phenyl-2H,6H-pyrimido[6,1-b] [1,3]thiazine-6,8(7H)-dione.
- 15 15. The use of a compound (I) according to Claim 1, or of a pharmaceutically acceptable salt thereof, for the production of a medicament according to any of Claims 8-10, wherein the said compound (I) is 9-phenyl-7-propyl-2H,6H-pyrimido[6,1-b] [1,3]thiazine-6,8(7H) -dione.

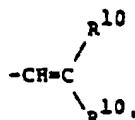
Patentansprüche

20 **Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE**

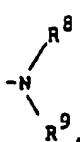
1. Verbindung, die durch die Formel (I) dargestellt wird, oder ein pharmakologisch annehmbares Salz davon:



30 worin R¹ (1) eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen oder eine Alkenylgruppe mit 2 bis 8 Kohlenstoffatomen, die mit den Gruppen Cyan, Carbamoyl, Pyridyl, Chinolyl, Hydroxy, C₁- bis C₄-Alkoxy, Amino, C₁- bis C₄-Alkyl, Carboxy, C₁- bis C₄-Alkoxy carbonyl oder C₂- bis C₆-Alkanoylamino substituiert sein können, (2) eine Aralkylgruppe, die durch Kombinieren einer Phenyl- oder Naphthylgruppe mit einer Alkylengruppe mit 1 bis 4 Kohlenstoffatomen erhalten wird, wobei die Phenyl- oder Naphthylgruppe mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl, Phenyl, o-Cyanphenyl, Methoxy, Ethoxy oder Nitro substituiert sein kann, oder (3) eine Phenyl- oder Naphthylgruppe, die mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, bedeutet; R² (1) Wasserstoff, (2) eine aliphatische Kohlenwasserstoffgruppe der Formel:



45 worin R¹⁰ eine Cyan-, Carbamoyl- oder C₁- bis C₄-Alkoxy carbonylgruppe bedeutet, R¹¹ eine C₁- bis C₈-Alkyl-, Phenyl-, Naphthyl-, Cyan-, Carbamoyl- oder C₁- bis C₄-Alkoxy carbonylgruppe bedeutet und R¹² Dimethylamino, Diethylamino, Morpholino, Piperidino oder Piperazino bedeutet, (3) eine Phenyl- oder Naphthylgruppe, die mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, (4) eine unsubstituierte oder substituierte Aminogruppe der Formel:



worin R⁸ und R⁹ jeweils Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen oder eine von einer Fettsäure

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abgeleitete Acylgruppe mit 1 bis 8 Kohlenstoffatomen sind, (5) eine Formylgruppe, (6) eine Nitrogruppe oder (7) eine Halogengruppe bedeutet; A eine gesättigte oder ungesättigte zweiwertige Kohlenwasserstoffkette mit 2 bis 4 Kohlenstoffatomen, die aus (1) einer Gruppe der Formel:



10 worin R³ (1) Wasserstoff, (2) C₁- bis C₄-Alkyl, das mit einem Halogenatom oder einer C₁- bis C₄-Alkylthio- oder Phenylthiogruppe substituiert sein kann, (3) -YR⁵, worin Y -O- oder -S- ist und R⁵ Wasserstoff, C₁- bis C₄-Alkyl oder eine Phenyl- oder Naphthylgruppe, die mit C₁- bis C₄-Alkyl-, C₁- bis C₄-Alkoxy oder Phenyl, das mit 1 bis 3 Halogenatomen oder einer von einer Fettsäure abgeleiteten Acylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, substituiert sein kann, ist, bedeutet, R⁴ Wasserstoff oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet und n eine ganze Zahl von 0 bis 2 bedeutet, (2) einer Gruppe der Formel:

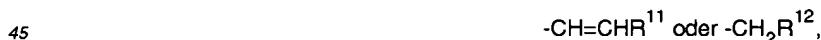


20 worin R¹⁵ und R¹⁶ Wasserstoff, C₁- bis C₄-Alkyl, -COOR¹⁷, worin R¹⁷ Wasserstoff oder C₁- bis C₄-Alkyl ist, oder -NHR¹⁸, worin R¹⁸ Wasserstoff, C₁- bis C₄-Alkyl oder C₁- bis C₄-Alkanoyl ist, bedeuten und n eine ganze Zahl von 0 bis 2 bedeutet, oder (3) einer Gruppe der Formel:



worin n eine ganze Zahl von 0 bis 2 bedeutet, ausgewählt ist, bedeutet; und m eine ganze Zahl von 0 bis 2 bedeutet.

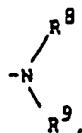
- 30 2. Verbindung gemäß Anspruch 1, worin R¹ eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen oder eine Alkenylgruppe mit 2 bis 8 Kohlenstoffatomen bedeutet.
3. Verbindung gemäß Anspruch 1, worin R¹ eine Aralkylgruppe, die durch Kombinieren einer Phenyl- oder Naphthylgruppe mit einer Alkylengruppe mit 1 bis 4 Kohlenstoffatomen erhalten wird, bedeutet.
- 35 4. Verbindung gemäß Anspruch 1, worin R¹ eine Phenyl- oder Naphthylgruppe bedeutet.
5. Verbindung gemäß Anspruch 1, worin R² eine Gruppe der Formel:



worin R¹⁰ eine Cyan-, Carbamoyl- oder C₁- bis C₄-Alkoxy carbonylgruppe bedeutet, R¹¹ eine C₁- bis C₈-Alkyl-, Phenyl-, Naphthyl-, Cyan-, Carbamoyl- oder C₁- bis C₄-Alkoxy carbonylgruppe bedeutet und R¹² Dimethylamino, Diethylamino, Morpholino, Piperidino oder Piperazino bedeutet, bedeutet.

- 50 6. Verbindung gemäß Anspruch 1, worin R² eine Phenyl- oder Naphthylgruppe, die mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, bedeutet.
7. Verbindung gemäß Anspruch 1, worin R² eine Gruppe der Formel:

5

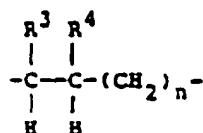


worin R⁸ und R⁹ jeweils Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen oder eine von einer Fettsäure abgeleitete Acylgruppe mit 1 bis 8 Kohlenstoffatomen sind, bedeutet.

10 8. Verbindung gemäß Anspruch 1, worin R² eine Halogengruppe bedeutet, die aus Fluor, Chlor, Brom und Iod ausgewählt ist.

9. Verbindung gemäß Anspruch 1, worin A durch die Formel:

15

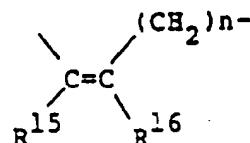


20 dargestellt ist, worin R³ (1) Wasserstoff, (2) C₁- bis C₄-Alkyl, das mit Halogen, C₁- bis C₄-Alkylthio oder Phenylthio substituiert sein kann, (3) -YR⁵, worin Y -O- oder -S- ist und R⁵ Wasserstoff, C₁- bis C₄-Alkyl oder Phenyl- oder Naphthyl, das mit C₁- bis C₄-Alkyl-, C₁- bis C₄-Alkoxy oder Phenyl, das mit 1 bis 3 Halogenatomen oder einer von einer Fettsäure abgeleiteten Acylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, substituiert sein kann, ist, bedeutet, R⁴ Wasserstoff oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet und n eine ganze Zahl von 0 bis 2 bedeutet.

25

10. Verbindung gemäß Anspruch 1, worin A durch die Formel:

30

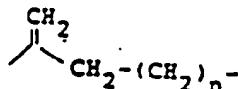


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dargestellt wird, worin R¹⁵ und R¹⁶ (1) Wasserstoff, (2) C₁- bis C₄-Alkyl, (3) -COOR¹⁷ (worin R¹⁷ Wasserstoff oder C₁- bis C₄-Alkyl ist) oder (4) -NHR¹⁸ (worin R¹⁸ Wasserstoff, C₁- bis C₄-Alkyl oder C₁- bis C₄-Alkanoyl ist) bedeuten und n eine ganze Zahl von 0 bis 2 bedeutet.

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11. Verbindung gemäß Anspruch 1, worin A durch die Formel:



dargestellt wird, worin n eine ganze Zahl von 0 bis 2 bedeutet.

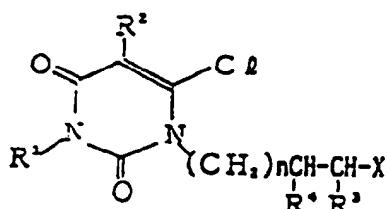
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12. Verbindung gemäß Anspruch 1, worin R¹ (1) eine Alkylgruppe mit 3 bis 8 Kohlenstoffatomen, die mit Cyan, Carbamoyl, Pyridyl, Chinolyl, Hydroxy, C₁- bis C₄-Alkoxy, Amino, C₁- bis C₄-Alkyl, Carboxy, C₁- bis C₄-Alkoxycarbonyl oder C₂- bis C₆-Alkanoylamino substituiert sein kann, oder (2) eine Aralkylgruppe, die durch Kombinieren einer Phenyl- oder Naphthylgruppe mit einer Alkylengruppe mit 1 bis 4 Kohlenstoffatomen erhalten wird, wobei die Phenyl- oder Naphthylgruppe mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Phenyl-, o-Cyanphenyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, bedeutet, R² eine Phenyl- oder Naphthylgruppe, die mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, bedeutet und A eine zweiwertige Kohlenwasserstoffkette mit 2 bis 3 Kohlenstoffatomen ist.

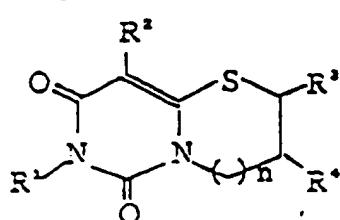
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13. Pharmakologisch annehmbares Salz einer durch die Formel (I) dargestellten Verbindung gemäß Anspruch 1, wobei das Salz ein anorganisches Salz, das aus dem Hydrochlorid, Hydrobromid, Sulfat, Nitrat und Phosphat ausgewählt ist, oder ein organisches Salz, das aus dem Acetat, Tartrat, Citrat, Fumarat und Maleat ausgewählt ist, ist.

14. Verbindung gemäß Anspruch 1, wobei die Zahl der Atome in der Kohlenstoffkette der Gruppe A vier ist.
15. Verbindung gemäß Anspruch 1, bei der es sich um 9-Phenyl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazin-6,8(7H)-dion handelt.
- 5 16. Verbindung gemäß Anspruch 1, bei der es sich um 7-Benzyl-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazin-6,8(7H)-dion handelt.
- 10 17. Verbindung gemäß Anspruch 1, bei der es sich um 7-(p-Chlorbenzyl)-9-phenyl-4H,6H-pyrimido[6,1-b][1,3]thiazin-6,8(7H)-dion handelt.
18. Verbindung gemäß Anspruch 1, bei der es sich um 7-Benzyl-9-phenyl-2H,6H-pyrimido[6,1-b][1,3]thiazin-6,8(7H)-dion handelt.
- 15 19. Verbindung gemäß Anspruch 1, bei der es sich um 9-Phenyl-7-propyl-2H,6H-pyrimido[6,1-b][1,3]thiazin-6,8(7H)-dion handelt.
- 20 20. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, umfassend das Umsetzen einer Verbindung der Formel (II):

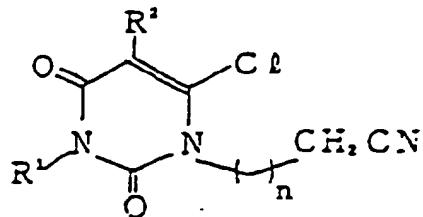


30 30 worin R¹ und R² wie in Anspruch 1 definiert sind, mit einem Schwefelreagenz, das aus NaSH, Na₂S und (NH₄)₂S ausgewählt ist, in einem organischen Lösungsmittel, so daß man eine Verbindung der Formel (III):

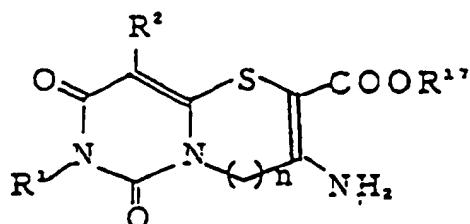


45 45 erhält, worin R³ Wasserstoff, eine C₁- bis C₄-Alkylgruppe, die mit einem Halogenatom oder einer C₁- bis C₄-Alkylthio- oder Phenylthiogruppe substituiert sein kann, -YR⁵ [worin Y -O- oder -S- ist und R⁵ Wasserstoff, eine C₁- bis C₄-Alkylgruppe oder eine Phenyl- oder Naphthylgruppe, die mit einem bis drei Halogenatomen oder einer von einer Fettsäure abgeleiteten C₁- bis C₄-Acylgruppe substituiert sein kann, ist] bedeutet, R⁴ Wasserstoff oder eine C₁- bis C₄-Alkylgruppe bedeutet und n eine ganze Zahl von 0 bis 2 bedeutet.

- 50 21. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, umfassend das Umsetzen einer Verbindung der Formel (XXVIII):

10 **XXVII**

mit 2-Thioglycolsäure in Gegenwart einer Base in einem organischen Lösungsmittel, so daß man eine Verbindung der Formel (XXIX) :

20 **XXIX**

25 erhält, worin R¹⁷ Wasserstoff oder C₁- bis C₄-Alkyl ist.

22. Verfahren zur Herstellung gemäß Anspruch 20 oder 21, das weiterhin eine Oxidation, Nitrierung, Reduktion, Hydrolyse, Alkylierung, Formylierung, Halogenierung, Dehydroxylierung, Acetalbildung, Thioacetalbildung, Kondensation, Wittig-Reaktion, Mannich-Reaktion, Amidierung, nucleophile Substitution, Dehydrochlorierung, Eliminierung oder Dealkylierung umfaßt.
23. Endothelin-hemmende Zusammensetzung, die eine wirksame Menge einer Verbindung gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon sowie gegebenenfalls einen oder mehrere pharmazeutisch annehmbare zusätzliche Bestandteile enthält.
24. IL-1-hemmende Zusammensetzung, die eine wirksame Menge einer Verbindung gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon sowie gegebenenfalls einen oder mehrere pharmazeutisch annehmbare zusätzliche Bestandteile enthält.
25. NGF-stimulierende Zusammensetzung, die eine wirksame Menge einer Verbindung gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon sowie gegebenenfalls einen oder mehrere pharmazeutisch annehmbare zusätzliche Bestandteile enthält.
26. Zusammensetzung gemäß einem der Ansprüche 23 bis 25, wobei die pharmazeutisch annehmbaren zusätzlichen Bestandteile Träger, Lösungsvermittler, Gleitmittel, Bindemittel, Dispergiermittel, Weichmacher und Verdünnungsmittel umfassen.
27. Verwendung einer Verbindung gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments zur Verhinderung der physiologischen Rolle der endothelialen Wirkung.
28. Verwendung einer Verbindung gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments zur Verhinderung der IL-1-Erzeugung.
29. Verwendung einer Verbindung gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments zur Stimulierung der NGF-Erzeugung.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung, die durch die Formel (I) dargestellt wird, oder eines pharmakologisch annehmbaren Salzes davon:

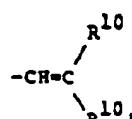
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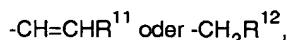
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worin R¹ (1) eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen oder eine Alkenylgruppe mit 2 bis 8 Kohlenstoffatomen, die mit den Gruppen Cyan, Carbamoyl, Pyridyl, Chinolyl, Hydroxy, C₁- bis C₄-Alkoxy, Amino, C₁- bis C₄-Alkyl, Carboxy, C₁- bis C₄-Alkoxy carbonyl oder C₂- bis C₆-Alkanoylamino substituiert sein können, (2) eine Aralkylgruppe, die durch Kombinieren einer Phenyl- oder Naphthylgruppe mit einer Alkylengruppe mit 1 bis 4 Kohlenstoffatomen erhalten wird, wobei die Phenyl- oder Naphthylgruppe mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl, Phenyl, o-Cyanphenyl, Methoxy, Ethoxy oder Nitro substituiert sein kann, oder (3) eine Phenyl- oder Naphthylgruppe, die mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, bedeutet; R² (1) Wasserstoff, (2) eine aliphatische Kohlenwasserstoffgruppe der Formel:

20

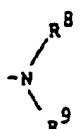


25



worin R¹⁰ eine Cyan-, Carbamoyl- oder C₁- bis C₄-Alkoxy carbonylgruppe bedeutet, R¹¹ eine C₁- bis C₈-Alkyl-, Phenyl-, Naphthyl-, Cyan-, Carbamoyl- oder C₁- bis C₄-Alkoxy carbonylgruppe bedeutet und R¹² Dimethylamino, Diethylamino, Morpholino, Piperidino oder Piperazino bedeutet, (3) eine Phenyl- oder Naphthylgruppe, die mit 1 bis 3 Halogenatomen, C₁- bis C₄-Alkyl-, Methoxy-, Ethoxy- oder Nitrogruppen substituiert sein kann, (4) eine unsubstituierte oder substituierte Aminogruppe der Formel:

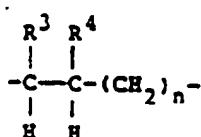
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worin R⁸ und R⁹ jeweils Wasserstoff, eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen oder eine von einer Fettsäure abgeleitete Acylgruppe mit 1 bis 8 Kohlenstoffatomen sind, (5) eine Formylgruppe, (6) eine Nitrogruppe oder (7) eine Halogengruppe bedeutet; A eine gesättigte oder ungesättigte zweiwertige Kohlenwasserstoffkette mit 2 bis 4 Kohlenstoffatomen, die aus (1) einer Gruppe der Formel:

40

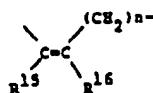


45

worin R³ (1) Wasserstoff, (2) C₁- bis C₄-Alkyl, das mit einem Halogenatom oder einer C₁- bis C₄-Alkylthio- oder Phenylthiogruppe substituiert sein kann, (3) -YR⁵, worin Y -O- oder -S- ist und R⁵ Wasserstoff, C₁- bis C₄-Alkyl oder eine Phenyl- oder Naphthylgruppe, die mit C₁- bis C₄-Alkyl-, C₁- bis C₄-Alkoxy oder Phenyl, das mit 1 bis 3 Halogenatomen oder einer von einer Fettsäure abgeleiteten Acylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, substituiert sein kann, ist, bedeutet, R⁴ Wasserstoff oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet und n eine ganze Zahl von 0 bis 2 bedeutet, (2) einer Gruppe der Formel:

50

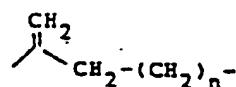
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worin R¹⁵ und R¹⁶ Wasserstoff, C₁- bis C₄-Alkyl, -COOR¹⁷, worin R¹⁷ Wasserstoff oder C₁- bis C₄-Alkyl ist, oder -NHR¹⁸, worin R¹⁸ Wasserstoff, C₁- bis C₄-Alkyl oder C₁- bis C₄-Alkanoyl ist, bedeuten und n eine ganze Zahl von 0 bis 2 bedeutet, oder (3) einer Gruppe der Formel:

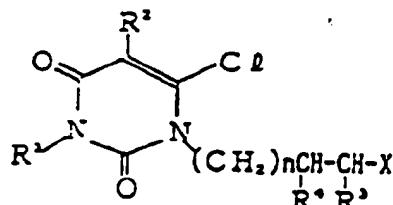
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worin n eine ganze Zahl von 0 bis 2 bedeutet, ausgewählt ist, bedeutet; und m eine ganze Zahl von 0 bis 2 bedeutet, wobei das Verfahren das Umsetzen einer Verbindung der Formel (II) :

15

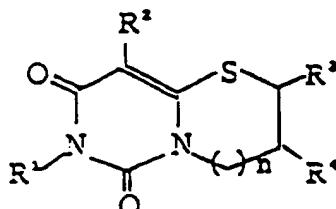


II

20

mit einem Schwefelreagenz, das aus NaSH, Na₂S und (NH₄)₂S ausgewählt ist, in einem organischen Lösungsmittel umfaßt, so daß man eine Verbindung der Formel (III):

25



III

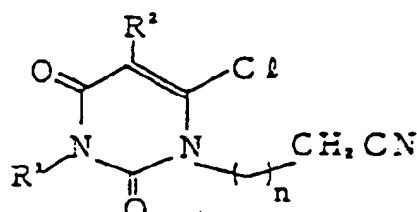
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erhält, worin R³ Wasserstoff, eine C₁- bis C₄-Alkylgruppe, die mit einem Halogenatom oder einer C₁- bis C₄-Alkylthio- oder Phenylthiogruppe substituiert sein kann, -YR⁵ [worin Y -O- oder -S- ist und R⁵ Wasserstoff, eine C₁- bis C₄-Alkylgruppe oder eine Phenyl- oder Naphthylgruppe, die mit einem bis drei Halogenatomen oder einer von einer Fettsäure abgeleiteten C₁- bis C₄-Acylgruppe substituiert sein kann, ist] bedeutet, R⁴ Wasserstoff oder eine C₁- bis C₄-Alkylgruppe bedeutet und n eine ganze Zahl von 0 bis 2 bedeutet.

35

2. Verfahren zur Herstellung einer Verbindung (I) gemäß Anspruch 1, umfassend das Umsetzen einer Verbindung der Formel (XXVII) :

45

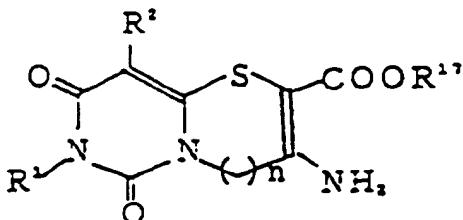


XXVII

50

mit einer Thioglycolsäure in Gegenwart einer Base in einem organischen Lösungsmittel, so daß man eine Verbindung der Formel (XXIX) :

55

**XXX**

erhält, worin R¹⁷ Wasserstoff oder C₁- bis C₄-Alkyl ist.

- 15
3. Verfahren zur Herstellung gemäß Anspruch 1 oder 2, das weiterhin eine Oxidation, Nitrierung, Reduktion, Hydrolyse, Alkylierung, Formylierung, Halogenierung, Dehydroxylierung, Acetalbildung, Thioacetalbildung, Kondensation, Wittig-Reaktion, Mannich-Reaktion, Amidierung, nucleophile Substitution, Dehydrochlorierung, Eliminierung oder Dealkylierung umfaßt.
- 20
4. Endothelin-hemmende Zusammensetzung, die eine wirksame Menge einer Verbindung (I), wie sie in Anspruch 1 definiert ist, oder eines pharmakologisch annehmbaren Salzes davon sowie gegebenenfalls einen oder mehrere pharmazeutisch annehmbare zusätzliche Bestandteile enthält.
- 25
5. IL-1-hemmende Zusammensetzung, die eine wirksame Menge einer Verbindung (I), wie sie in Anspruch 1 definiert ist, oder eines pharmakologisch annehmbaren Salzes davon sowie gegebenenfalls einen oder mehrere pharmazeutisch annehmbare zusätzliche Bestandteile enthält.
- 30
6. NGF-stimulierende Zusammensetzung, die eine wirksame Menge einer Verbindung (I), wie sie in Anspruch 1 definiert ist, oder eines pharmakologisch annehmbaren Salzes davon sowie gegebenenfalls einen oder mehrere pharmazeutisch annehmbare zusätzliche Bestandteile enthält.
- 35
7. Zusammensetzung gemäß einem der Ansprüche 4 bis 6, wobei die pharmazeutisch annehmbaren zusätzlichen Bestandteile aus Trägern, Lösungsvermittlern, Gleitmitteln, Bindemitteln, Dispergiermitteln, Weichmachern und Verdünnungsmitteln ausgewählt sind.
- 40
8. Verwendung einer Verbindung (I), wie sie in Anspruch 1 definiert ist, oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments zur Verhinderung der physiologischen Rolle der endothelialen Wirkung.
- 45
9. Verwendung einer Verbindung (I), wie sie in Anspruch 1 definiert ist, oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments zur Verhinderung der IL-1-Erzeugung.
- 50
10. Verwendung einer Verbindung (I), wie sie in Anspruch 1 definiert ist, oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments zur Stimulierung der NGF-Erzeugung.
- 55
11. Verwendung einer Verbindung (I) gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments gemäß einem der Ansprüche 8-10, wobei es sich bei der Verbindung (I) um 9-Phenyl-7-propyl-4H,6H-pyrimido[6,1-b] [1,3]thiazin-6,8(7H)-dion handelt.
12. Verwendung einer Verbindung (I) gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments gemäß einem der Ansprüche 8-10, wobei es sich bei der Verbindung (I) um 7-Benzyl-9-phenyl-4H,6H-pyrimido[6,1-b] [1,3]thiazin-6,8(7H)-dion handelt.
13. Verwendung einer Verbindung (I) gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon zur Herstellung eines Medikaments gemäß einem der Ansprüche 8-10, wobei es sich bei der Verbindung (I) um 7-(p-Chlorbenzyl)-9-phenyl-4H,6H-pyrimido[6,1-b] [1,3]thiazin-6,8(7H)-dion handelt.
14. Verwendung einer Verbindung (I) gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon

zur Herstellung eines Medikaments gemäß einem der Ansprüche 8-10, wobei es sich bei der Verbindung (I) um 7-Benzyl-9-phenyl-2H,6H-pyrimido[6,1-b] [1,3]thiazin-6,8(7H)-dion handelt.

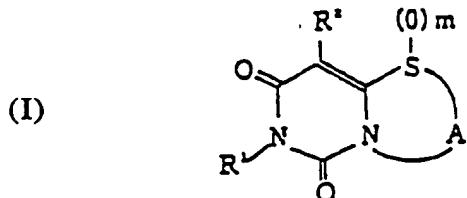
15. Verwendung einer Verbindung (I) gemäß Anspruch 1 oder eines pharmakologisch annehmbaren Salzes davon
 5 zur Herstellung eines Medikaments gemäß einem der Ansprüche 8-10, wobei es sich bei der Verbindung (I) um 9-Phenyl-7-propyl-2H,6H-pyrimido[6,1-b] [1,3]thiazin-6,8(7H)-dion handelt.

Revendications

10

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

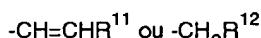
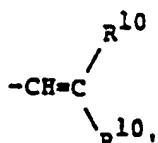
1. Composé représenté par la formule (I), ou un sel pharmacologiquement acceptable de celui-ci :



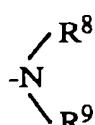
20 dans laquelle

R¹ représente (1) un groupe alkyle comportant de 1 à 8 atomes de carbone ou un groupe alcényle comportant de 2 à 8 atomes de carbone et pouvant être substitué par des groupes cyano, carbamoyle, pyridyle, quinolyle, hydroxyle, alcoxy en C₁₋₄, amino, alkyle en C₁₋₄, carboxyle, (alcoxy en C₁₋₄)-carbonyle ou (alcanoyle en C₂₋₆)-amino, (2) un groupe aralkyle obtenu par combinaison d'un groupe phényle ou naphtyle et d'un groupe alkylène comportant de 1 à 4 atomes de carbone dans lequel le groupe phényle ou naphtyle peuvent être substitués par 1 à 3 atomes d'halogène, groupes alkyle en C₁₋₄, phényle, o-cyanophényle, méthoxy, éthoxy ou nitro, ou (3) un groupe phényle ou naphtyle pouvant être substitué par 1 à 3 atomes d'halogène, un groupe alkyle en C₁₋₄, méthoxy, éthoxy ou nitro,

30 R² représente (1) un atome d'hydrogène, (2) un groupe hydrocarboné aliphatique de formule :

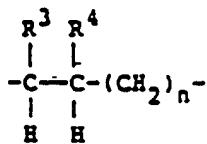


dans laquelle R¹⁰ représente un groupe cyano, carbamoyle ou (alcoxy en C₁₋₄)-carbonyle, R¹¹ représente un groupe alkyle en C₁₋₈, phényle, naphtyle, cyano, carbamoyle ou (alcoxy en C₁₋₄)-carbonyle, et R¹² représente un groupe diméthylamino, diéthylamino, morpholino, pipéridino ou pipérazino, (3) un groupe phényle ou naphtyle pouvant être substitué par 1 à 3 atomes d'halogène, un groupe alkyle en C₁₋₄, méthoxy, éthoxy ou nitro, (4) un groupe amino non substitué ou substitué de formule



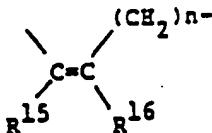
50 dans laquelle R⁸ et R⁹ représentent chacun un atome d'hydrogène, un groupe alkyle comportant de 1 à 8 atomes de carbone ou un groupe acyle dérivé d'un acide gras comportant de 1 à 8 atomes de carbone, (5) un groupe formyle, (6) un groupe nitro ou (7) un groupe halogéno; A représente une chaîne hydrocarbonée divalente saturée ou insaturée comportant de 2 à 4 atomes de carbone choisie parmi

55 (1) un groupe de formule

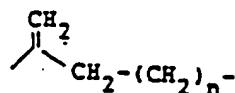


dans laquelle R^3 représente (1) un atome d'hydrogène, (2) un groupe alkyle en C_{1-4} pouvant être substitué par un atome d'halogène ou un groupe alkylthio en C_{1-4} ou phénylthio, (3) un groupe $-\text{YR}^5$ dans lequel Y est un groupe $-\text{O-}$ ou $-\text{S-}$ et R^5 représente un atome d'hydrogène, un groupe alkyle en C_{1-4} ou un groupe phényle ou naphtyle pouvant être substitué par un groupe alkyle en C_{1-4} , alcoxy en C_{1-4} ou phényle, qui à son tour peut être substitué par 1 à 3 atomes d'halogène, ou un groupe acyle dérivé d'un acide gras comportant de 1 à 4 atomes de carbone, R^4 représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone, et n représente un nombre entier compris entre 0 et 2,

(2) un groupe de formule

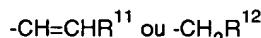
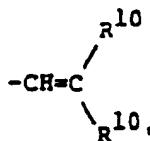


20 dans laquelle R^{15} et R^{16} représentent un atome d'hydrogène, un groupe alkyle en C_{1-4} , $-\text{COOR}^{17}$, où R^{17} est un atome d'hydrogène, un groupe alkyle en C_{1-4} ou un groupe $-\text{NHR}^{18}$, où R^{18} est un atome d'hydrogène, un groupe alkyle en C_{1-4} ou alcanoyle en C_{1-4} , et n représente un nombre entier de 0 à 2 ou (3) un groupe de formule :



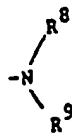
dans laquelle n représente un nombre entier de 0 à 2 et m un nombre entier de 0 à 2.

- 30 2. Composé conforme à la revendication 1 dans lequel R^1 représente un groupe alkyle en C_{1-8} ou un groupe alcényle en C_{2-8} .
3. Composé conforme à la revendication 1 dans lequel R^1 représente un groupe aralkyle obtenu par combinaison d'un groupe phényle ou naphtyle et d'un groupe alkylène comportant de 1 à 4 atomes de carbone.
- 35 4. Composé conforme à la revendication 1 dans lequel R^1 représente un groupe phényle ou naphtyle.
5. Composé conforme à la revendication 1 dans lequel R^2 représente un groupe de formule :



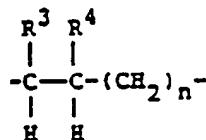
dans laquelle R^{10} représente un groupe cyano, carbamoyle ou (alcoxy en C_{1-4})-carbonyle, R^{11} représente un groupe alkyle en C_{1-8} , phényle, naphtyle, cyano, carbamoyle ou (alcoxy en C_{1-4})-carbonyle, et R^{12} représente un groupe diméthylamino, diéthylamino, morpholino, pipéridino ou pipérazino.

- 50 6. Composé conforme à la revendication 1 dans lequel R^2 représente un groupe phényle ou naphtyle pouvant être substitué par 1 à 3 atomes d'halogène ou groupes alkyle en C_{1-4} , méthoxy, éthoxy ou nitro.
7. Composé conforme à la revendication 1 dans lequel R^2 représente un groupe de formule



dans laquelle R⁸ et R⁹ représentent chacun un atome d'hydrogène, un groupe alkyle en C₁₋₈ ou un groupe acyle dérivé d'un acide gras comportant de 1 à 8 atomes de carbone.

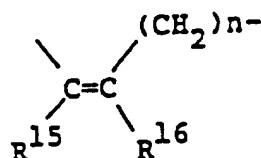
- 10 8. Composé conforme à la revendication 1 dans lequel R² représente un groupe halogéno choisi parmi le fluor, le chlore, le brome et l'iode.
9. Composé conforme à la revendication 1 dans lequel A représente un résidu de formule



20 dans laquelle R³ représente

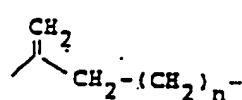
- (1) un atome d'hydrogène,
- (2) un groupe alkyle en C₁₋₄ pouvant être substitué par un atome d'halogène ou un groupe alkylthio en C₁₋₄ ou phénylthio,
- (3) un groupe -YR⁵ dans lequel Y représente un -O- ou -S- et R⁵ est un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou un groupe phényle ou naphtyle pouvant être substitués par un groupe alkyle en C₁₋₄, alcoxy en C₁₋₄ ou phényle, qui à son tour peut être substitué par 1 à 3 atomes d'halogène, ou un groupe acyle dérivé d'un acide gras comportant de 1 à 4 atomes de carbone, R⁴ représente un atome d'hydrogène ou un groupe alkyle en C₁₋₄, et n représente un nombre entier compris entre 0 et 2.

- 30 10. Composé conforme à la revendication 1 dans lequel A représente un groupe de formule



40 dans laquelle R¹⁵ et R¹⁶ représentent (1) un atome d'hydrogène, (2) un groupe alkyle en C₁₋₄, (3) un groupe -COOR¹⁷ (où R¹⁷ est un atome d'hydrogène ou un groupe alkyle en C₁₋₄), ou (4) un groupe -NHR¹⁸ (où R¹⁸ est un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou alcanoyle en C₁₋₄), et n représente un nombre entier compris entre 0 et 2.

- 45 11. Composé conforme à la revendication 1 dans lequel A représente un groupe de formule

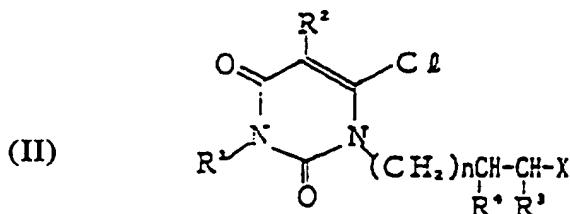


50 dans laquelle n est un nombre entier compris entre 0 et 2.

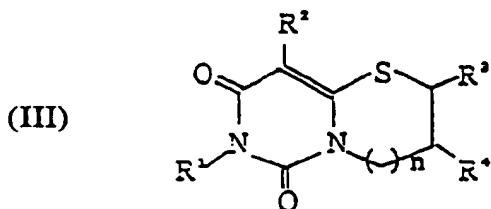
- 55 12. Composé conforme à la revendication 1 dans lequel R¹ représente (1) un groupe alkyle comportant de 3 à 8 atomes de carbone pouvant être substitués par un groupe cyano, carbamoyle, pyridyle, quinolyle, hydroxyle, alcoxy en C₁₋₄, amino, alkyle en C₁₋₄, carboxyle, (alcoxy en C₁₋₄)-carbonyle ou (alcanoyl en C₂₋₆)-amino, ou (2) un groupe aralkyle obtenu par combinaison d'un groupe phényle dans lequel et d'un groupe alkylène comportant de 1 à 4 atomes de carbone dans lequel le groupe phényle ou naphtyle peuvent être substitués par 1 à 3 atomes d'halogène, groupes alkyle en C₁₋₄, phényle, o-cyanophényle, méthoxy, substitué nitro; R² représente un groupe phényle ou naphtyle pouvant être substitué par 1 à 3 atomes d'halogène ou groupes alkyle en C₁₋₄, méthoxy,

éthoxy ou nitro, et A est une chaîne hydrocarbonée divalente comportant de 2 à 3 atomes de carbone.

13. Sel pharmacologiquement acceptable d'un composé représenté par la formule (I) conforme à la revendication 1 dans lequel le sel est un sel minéral choisi parmi les chlorhydrate, bromhydrate, sulfate, nitrate et phosphate, ou un sel organique choisi parmi les acétate, tartrate, citrate, fumarate et maléate.
- 5
14. Composé conforme à la revendication 1 dans lequel le nombre de chaînes carbonées du groupe A est 4.
15. Composé conforme à la revendication 1 qui est la 9-phényl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 10
16. Composé conforme à la revendication 1 qui est la 7-benzyl-9-phényl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 15
17. Composé conforme à la revendication 1 qui est la 7-(*p*-chlorobenzyl)-9-phényl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 20
18. Composé conforme à la revendication 1 qui est la 7-benzyl-9-phényl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
19. Composé conforme à la revendication 1 qui est la 9-phényl-7-propyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 25
20. Procédé de préparation d'un composé conforme à la revendication 1 comprenant la réaction d'un composé de formule (II) :

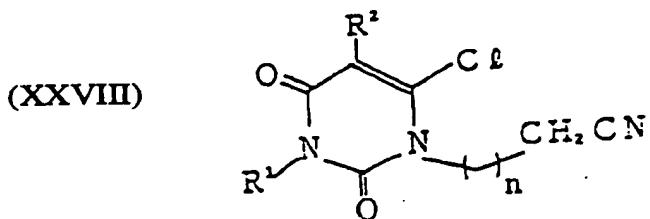


35 dans laquelle R¹ et R² sont définis dans la revendication 1, avec un réactif soufré choisi parmi NₐSH, Nₐ₂S et (NH₄)₂S dans un solvant organique afin d'obtenir un composé de formule (III) :

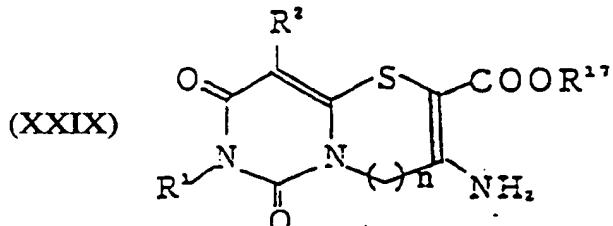


45 dans laquelle R³ représente un atome d'hydrogène un groupe alkyle en C₁-₄ pouvant être substitué par un atome d'halogène ou un groupe alkylthio en C₁-₄ ou un groupe phénylthio, -YR⁵ [où Y est un groupe -O- ou -S-, et R⁵ est un atome d'hydrogène, un groupe alkyle en C₁-₄ ou un groupe phényle ou naphtyle pouvant être substitués par 1 à 3 atomes d'halogène ou un groupe acyle en C₁-₄ dérivé d'un acide gras, R⁴ est un atome d'hydrogène ou un groupe alkyle en C₁-₄ et n représente un nombre entier compris entre 0 et 2].

- 50
21. Procédé de préparation d'un composé (I) conforme à la revendication 1 qui comprend le fait de faire réagir un composé de formule (XXVIII) :



¹⁰ avec de l'acide 2-thioglycolique en présence d'une base dans un solvant organique afin d'obtenir un composé de formule (XXIX) :



dans laquelle R₁₇ est un atome d'hydrogène ou un groupe alkyle en C₁₋₄.

- 25 22. Procédé de préparation conforme à la revendication 20 ou 21, comprenant en outre une étape d'oxydation, de nitration, de réduction, d'hydrolyse, d'alkylation, de formylation, d'halogénéation, de déshydroxylation, d'acétalisation, de thioacétalisation, de condensation, de réaction de Wittig, de réaction de Mannich, d'amidation, de substitution nucléophile, de déshydrochloration, d'élimination ou de désalkylation.

30 23. Composition inhibant l'endothéline et contenant une quantité efficace d'un composé conforme à la revendication 1 ou un sel pharmaceutiquement acceptable de ce composé et éventuellement un ou plusieurs composants additionnels pharmaceutiquement acceptables.

35 24. Composition inhibant l'IL-1 et contenant une quantité efficace d'un composé conforme à la revendication 1 ou un sel pharmaceutiquement acceptable d'un tel composé et éventuellement un ou plusieurs composants additionnels pharmaceutiquement acceptables.

40 25. Composition stimulant le NGF et contenant une quantité efficace d'un composé conforme à la revendication 1 ou un sel pharmaceutiquement acceptable d'un tel composé et éventuellement un ou plusieurs composants additionnels pharmaceutiquement acceptables.

26. Composition conforme à une quelconque des revendications 23 à 25 dans laquelle les composants additionnels pharmaceutiquement acceptables englobent des véhicules, agents de délitement, lubrifiants, liants, agents de dispersion, plastifiants et diluants.

45 27. Utilisation d'un composé conforme à la revendication 1 ou d'un sel pharmacologiquement acceptable d'un tel composé pour la fabrication d'un médicament pour la prévention du rôle physiologique de l'action endothéliale.

28. Utilisation d'un composé conforme à la revendication 1 ou d'un sel pharmacologiquement acceptable d'un tel composé pour la fabrication d'un médicament pour la prévention de la production de l'IL-1.

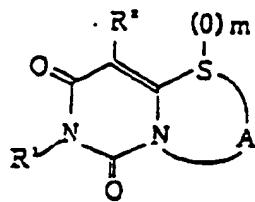
50 29. Utilisation d'un composé conforme à la revendication 1 ou d'un sel pharmacologiquement acceptable d'un tel composé pour la fabrication d'un médicament pour la stimulation de la production de NGF.

Revendications pour l'Etat contractant suivant : ES

- 55 1. Procédé de préparation d'un composé représenté par la formule (I), ou un sel pharmacologiquement acceptable de celui-ci :

5

(I)



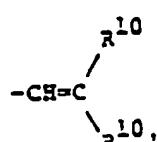
dans laquelle

10 R¹ représente (1) un groupe alkyle comportant de 1 à 8 atomes de carbone ou un groupe alcényle comportant de 2 à 8 atomes de carbone et pouvant être substitué par des groupes cyano, carbamoyle, pyridyle, quinolyle, hydroxyle, alcoxy en C₁₋₄, amino, alkyle en C₁₋₄, carboxyle, (alcoxy en C₁₋₄)-carbonyle ou (alcanoyle en C₂₋₆)-amino, (2) un groupe aralkyle obtenu par combinaison d'un groupe phényle ou naphtyle et d'un groupe alkylène comportant de 1 à 4 atomes de carbone dans lequel le groupe phényle ou naphtyle peuvent être substitués par 1 à 3 atomes d'halogène, groupes alkyle en C₁₋₄, phényle, o-cyanophényle, méthoxy, éthoxy ou nitro, ou (3) un groupe phényle ou naphtyle pouvant être substitué par 1 à 3 atomes d'halogène, un groupe alkyle en C₁₋₄, méthoxy, éthoxy ou nitro,

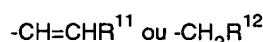
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R² représente (1) un atome d'hydrogène, (2) un groupe hydrocarboné aliphatique de formule :

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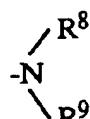
25



30

dans laquelle R¹⁰ représente un groupe cyano, carbamoyle ou (alcoxy en C₁₋₄)-carbonyle, R¹¹ représente un groupe alkyle en C₁₋₈ phényle, naphtyle, cyano, carbamoyle ou (alcoxy en C₁₋₄)-carbonyle, et R¹² représente un groupe diméthylamino, diéthylamino, morpholino, pipéridino ou pipérazino, (3) un groupe phényle ou naphtyle pouvant être substitué par 1 à 3 atomes d'halogène, un groupe alkyle en C₁₋₄, méthoxy, éthoxy ou nitro, (4) un groupe amino non substitué ou substitué de formule

35

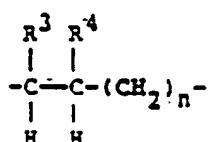


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dans laquelle R⁸ et R⁹ représentent chacun un atome d'hydrogène, un groupe alkyle comportant de 1 à 8 atomes de carbone ou un groupe acyle dérivé d'un acide gras comportant de 1 à 8 atomes de carbone, (5) un groupe formyle, (6) un groupe nitro ou (7) un groupe halogéno; A représente une chaîne hydrocarbonée divalente saturée ou insaturée comportant de 2 à 4 atomes de carbone choisie parmi

(1) un groupe de formule

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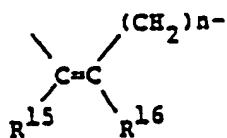
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dans laquelle R³ représente (1) un atome d'hydrogène, (2) un groupe alkyle en C₁₋₄ pouvant être substitué par un atome d'halogène ou un groupe alkylthio en C₁₋₄ ou phénylthio, (3) un groupe -YR⁵ dans lequel Y est un groupe -O- ou -S- et R⁵ représente un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou un groupe phényle ou naphtyle pouvant être substitué par un groupe alkyle en C₁₋₄, alcoxy en C₁₋₄ ou phényle, qui à son tour peut être substitué par 1 à 3 atomes d'halogène, ou un groupe acyle dérivé d'un acide gras comportant de 1 à 4 atomes de carbone, R⁴ représente un atome d'hydrogène ou un groupe alkyle comportant de 1 à 4 atomes de carbone, et n représente un nombre entier compris entre 0 et 2,

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(2) un groupe de formule

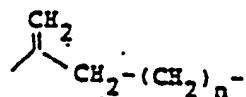
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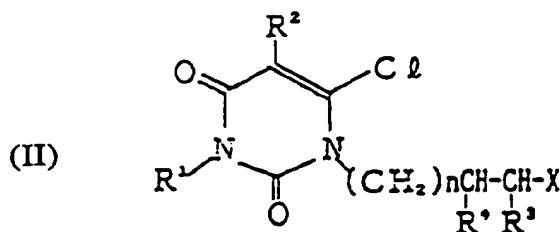
dans laquelle R¹⁵ et R¹⁶ représentent un atome d'hydrogène, un groupe alkyle en C₁₋₄, -COOR¹⁷, où R¹⁷ est un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou un groupe -NHR¹⁸, où R¹⁸ est un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou alcanoyle en C₁₋₄, et n représente un nombre entier de 0 à 2 ou (3) un groupe de formule :

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dans laquelle n représente un nombre entier de 0 à 2 et m un nombre entier de 0 à 2, lequel procédé comprend la réaction d'un composé de formule (II) :

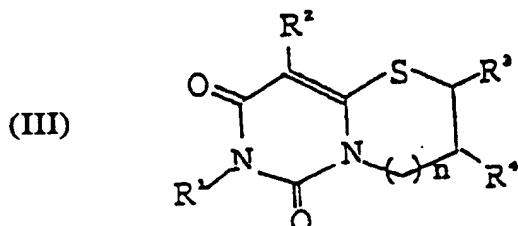
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avec un réactif soufré choisi parmi N_aSH, N_{a2}S et (NH₄)₂S dans un solvant organique afin d'obtenir un composé de formule (III) :

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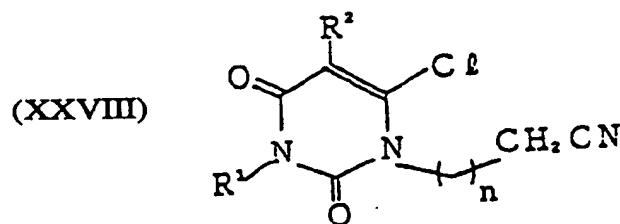
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dans laquelle R³ représente un atome d'hydrogène, un groupe alkyle en C₁₋₄ pouvant être substitué par un atome d'halogène ou un groupe alkylthio en C₁₋₄ ou un groupe phénylthio, -YR⁵ [où Y est un groupe -O- ou -S-, et R⁵ est un atome d'hydrogène, un groupe alkyle en C₁₋₄ ou un groupe phényle ou naphtyle pouvant être substitués par 1 à 3 atomes d'halogène ou un groupe acyle en C₁₋₄ dérivé d'un acide gras, R⁴ est un atome d'hydrogène ou un groupe alkyle en C₁₋₄ et n représente un nombre entier compris entre 0 et 2].

2. Procédé de préparation d'un composé (I) conforme à la revendication 1 qui comprend le fait de faire réagir un composé de formule (XXVIII) :

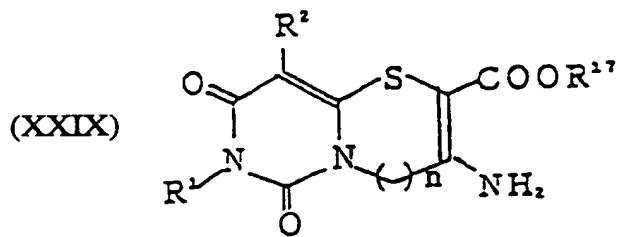
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avec de l'acide thioglycolique en présence d'une base dans un solvant organique afin d'obtenir un composé de formule (XXIX) :

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dans laquelle R¹⁷ est un atome d'hydrogène ou un groupe alkyle en C₁₋₄.

- 5 3. Procédé de préparation conforme à la revendication 1 ou 2, comprenant en outre une étape d'oxydation, de nitration, de réduction, d'hydrolyse, d'alkylation, de formylation, d'halogénéation, de déshydroxylation, d'acétalisation, de thioacétalisation, de condensation, de réaction de Wittig, de réaction de Mannich, d'amidation, de substitution nucléophile, de déshydrochloration, d'élimination ou de désalkylation.
- 10 4. Composition inhibant l'endothélial et contenant une quantité efficace d'un composé (I) défini dans la revendication 1 ou un sel pharmaceutiquement acceptable de ce composé et éventuellement un ou plusieurs composants additionnels pharmaceutiquement acceptables.
- 15 5. Composition inhibant l'IL-1 et contenant une quantité efficace d'un composé (I) défini dans la revendication 1 ou un sel pharmaceutiquement acceptable d'un tel composé et éventuellement un ou plusieurs composants additionnels pharmaceutiquement acceptables.
- 20 6. Composition stimulant le NGF et contenant une quantité efficace d'un composé (I) défini dans la revendication 1 ou un sel pharmaceutiquement acceptable d'un tel composé et éventuellement un ou plusieurs composants additionnels pharmaceutiquement acceptables.
- 25 7. Composition conforme à une quelconque des revendications 4 à 6 dans laquelle les composants additionnels pharmaceutiquement acceptables sont choisis parmi les véhicules, agents de délitement, lubrifiants, liants, agents de dispersion, plastifiants et diluants.
- 30 8. Utilisation d'un composé (I) défini dans la revendication 1 ou d'un sel pharmacologiquement acceptable d'un tel composé pour la fabrication d'un médicament pour la prévention du rôle physiologique de l'action endothéliale.
- 35 9. Utilisation d'un composé (I) défini dans la revendication 1 ou d'un sel pharmacologiquement acceptable d'un tel composé pour la fabrication d'un médicament pour la prévention de la production d'IL-1.
- 40 10. Utilisation d'un composé (I) défini dans la revendication 1 ou d'un sel pharmacologiquement acceptable d'un tel composé pour la fabrication d'un médicament pour la stimulation de la production de NGF.
- 45 11. Utilisation d'un composé (I) conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé pour la fabrication d'un médicament conforme à une quelconque des revendications 8 à 10 dans lequel ledit composé (I) est la 9-phényl-7-propyl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 50 12. Utilisation d'un composé (I) conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé pour la fabrication d'un médicament conforme à une quelconque des revendications 8 à 10 dans lequel ledit composé (I) est la 7-benzyl-9-phényl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 55 13. Utilisation d'un composé (I) conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé pour la fabrication d'un médicament conforme à une quelconque des revendications 8 à 10 dans lequel ledit composé (I) est la 7-(p-chlorobenzyl)-9-phényl-4H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 60 14. Utilisation d'un composé (I) conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé pour la fabrication d'un médicament conforme à une quelconque des revendications 8 à 10 dans lequel ledit composé (I) est la 7-benzyl-9-phényl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.
- 65 15. Utilisation d'un composé (I) conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel

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composé pour la fabrication d'un médicament conforme à une quelconque des revendications 8 à 10 dans lequel
ledit composé (I) est la 9-phényl-7-propyl-2H,6H-pyrimido[6,1-b][1,3]thiazine-6,8(7H)-dione.

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